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<p>(21) International Application Number: <b>PCT/US00/11951</b>  (22) International Filing Date: <b>3 May 2000 (03.05.00)</b>  (30) Priority Data:  <table border="0"> <tr> <td>60/132,194</td> <td>3 May 1999 (03.05.99)</td> <td>US</td> </tr> <tr> <td>60/132,189</td> <td>3 May 1999 (03.05.99)</td> <td>US</td> </tr> <tr> <td>60/132,185</td> <td>3 May 1999 (03.05.99)</td> <td>US</td> </tr> </table>  (71) Applicant (for all designated States except US): <b>SMITHKLINE BEECHAM CORPORATION [US/US]; One Franklin Plaza, Philadelphia, PA 19103 (US).</b>  (72) Inventors; and (75) Inventors/Applicants (for US only): <b>LUENGO, Juan I. [ES/US]; 701 Pondview Drive, Audubon, PA 19403 (US). PRICE, Alan, Thomas [US/US]; 2201 Eland Downe, Phoenixville, PA 19460 (US). SHAW, Antony [GB/US]; 713 Jacques Circle, Chester Springs, PA 19425 (US). WIGGALL, Kenneth [GB/US]; 910 Brookmont Circle, Malvern, PA 19355 (US).</b></p>	60/132,194	3 May 1999 (03.05.99)	US	60/132,189	3 May 1999 (03.05.99)	US	60/132,185	3 May 1999 (03.05.99)	US	<p>(74) Agents: <b>DUSTMAN, Wayne, J. et al.; SmithKline Beecham Corporation, Corporate Intellectual Property, UW2220, 709 Swedeland Road, P.O. Box 1539, King of Prussia, PA 19406-0939 (US).</b>  (81) Designated States: <b>AU, CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</b>  Published <i>With international search report.</i></p>
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<p>(54) Title: <b>CXCR-4 RECEPTOR ANTAGONISTS - THROMBOPOIETIN MIMETICS</b>  (57) Abstract  Invented are substituted cyclam derivatives, pharmaceutical compositions containing these compounds, the use of these compounds as CXCR-4 receptor antagonists and to use of these compounds as thrombopoietin (TPO) mimetics.</p>										

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## CXCR-4 RECEPTOR ANTAGONISTS - THROMBOPOIETIN MIMETICS

### FIELD OF THE INVENTION

The present invention relates to cyclam derivatives, pharmaceutical compositions containing these compounds, the use of these compounds as CXCR-4 receptor antagonists and to  
5 use of these compounds as promoters of thrombopoiesis and megakaryocytopoiesis.

### BACKGROUND OF THE INVENTION

The CXCR-4 receptor, originally known as LESTR/fusin, was shown to be the receptor for the  $\alpha$  or CXC chemokine stromal cell-derived factor-1 (SDF-1) in 1996 and renamed at this time. SDF-1 appears to be specific for CXCR-4 and mediates its chemotactic effects *via* this  
10 receptor. The CXCR-4 receptor is widely expressed in a variety of cell types and is implicated in a range of inflammatory responses mediated by SDF-1.

The widespread distribution of the receptor leads to its involvement in a number of disease areas including bacterial, fungal and protozoan infections, pain, cancer, diabetes, obesity, anorexia, bulimia, asthma, allergies, Parkinson's disease, acute heart failure, hypotension,  
15 hypertension, atherosclerosis, disease states involving angiogenesis, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers, benign prostatic hypertrophy, migraine, vomiting, psychotic and neurological disorders (e.g. anxiety, schizophrenia, manic depression, depression, delirium, dementia, mental retardation) and dyskinesias (Huntington's disease and Gilles de la Tourette's syndrome), injured or severed spinal cord and other injury  
20 related disease states.

In addition, CXCR-4 has been identified as the co-receptor used by T-tropic HIV-1 viral strains to infect cells, and antagonists of the receptor may therefore be useful in the treatment of late stage HIV infection and AIDS.

Based on the foregoing, CXCR-4 receptor antagonists offer a unique approach toward  
25 decreasing the pathophysiology associated with the aforementioned diseases.

As disclosed herein it has unexpectedly been discovered that certain cyclam derivatives are effective as CXCR-4 receptor antagonists.

Megakaryocytes are bone marrow-derived cells, which are responsible for producing  
30 circulating blood platelets. Although comprising <0.25% of the bone marrow cells in most species, they have >10 times the volume of typical marrow cells. See Kuter et al. Proc. Natl. Acad. Sci. USA 91: 11104-11108 (1994). Megakaryocytes undergo a process known as endomitosis whereby they replicate their nuclei but fail to undergo cell division and thereby give rise to polyploid cells. In response to a decreased platelet count, the endomitotic rate increases,  
35 higher ploidy megakaryocytes are formed, and the number of megakaryocytes may increase up to 3-fold. See Harker J. Clin. Invest. 47: 458-465 (1968). In contrast, in response to an

elevated platelet count, the endomitotic rate decreases, lower ploidy megakaryocytes are formed, and the number of megakaryocytes may decrease by 50%.

The exact physiological feedback mechanism by which the mass of circulating platelets regulates the endomitotic rate and number of bone marrow megakaryocytes is not known. The circulating thrombopoietic factor involved in mediating this feedback loop is now thought to be thrombopoietin (TPO). More specifically, TPO has been shown to be the main humoral regulator in situations involving thrombocytopenia. See, e.g., Metcalf *Nature* 369:519-520 (1994). TPO has been shown in several studies to increase platelet counts, increase platelet size, and increase isotope incorporation into platelets of recipient animals. Specifically, TPO is thought to affect megakaryocytopoiesis in several ways: (1) it produces increases in megakaryocyte size and number; (2) it produces an increase in DNA content, in the form of polyploidy, in megakaryocytes; (3) it increases megakaryocyte endomitosis; (4) it produces increased maturation of megakaryocytes; and (5) it produces an increase in the percentage of precursor cells, in the form of small acetylcholinesterase-positive cells, in the bone marrow.

Because platelets (thrombocytes) are necessary for blood clotting and when their numbers are very low a patient is at risk of death from catastrophic hemorrhage, TPO has potential useful application in both the diagnosis and the treatment of various hematological disorders, for example, diseases primarily due to platelet defects. Ongoing clinical trials with TPO have indicated that TPO can be administered safely to patients. In addition, recent studies have provided a basis for the projection of efficacy of TPO therapy in the treatment of thrombocytopenia, and particularly thrombocytopenia resulting from chemotherapy, radiation therapy, or bone marrow transplantation as treatment for cancer or lymphoma. See e.g., McDonald (1992) *Am. J. Ped. Hematology/Oncology* 14: 8-21 (1992).

The gene encoding TPO has been cloned and characterized. See Kuter et al., *Proc. Natl. Acad. Sci. USA* 91: 11104-11108 (1994); Barley et al., *Cell* 77: 1117-1124 (1994); Kaushansky et al., *Nature* 369:568-571 (1994); Wendling et al., *Nature* 369: 571-574 (1994); and Sauvage et al., *Nature* 369: 533-538 (1994). Thrombopoietin is a glycoprotein with two distinct regions separated by a potential Arg-Arg cleavage site. The amino-terminal region is highly conserved in man and mouse, and has some homology with erythropoietin and interferon-alpha and interferon-beta. The carboxy-terminal region shows wide species divergence.

The DNA sequences and encoded peptide sequences for human TPO receptor (TPO-R; also known as c-mpl) have been described. See, Vigon et al. *Proc. Natl. Acad. Sci. USA* 89: 5640-5644 (1992). TPO-R is a member of the haematopoietin growth factor receptor family, a family characterized by a common structural design of the extracellular domain, including for conserved C residues in the N-terminal portion and a WSXWS motif close to the transmembrane region. See Bazan *Proc. Natl. Acad. Sci. USA* 87: 6934-6938 (1990). Evidence that this

receptor plays a functional role in hematopoiesis includes observations that its expression is restricted to spleen, bone marrow, or fetal liver in mice (see Souyri et al. Cell 63: 1137-1147 (1990)) and to megakaryocytes, platelets, and CD34<sup>+</sup> cells in humans (see Methia et al. Blood 82: 1395-1401 (1993)). Further evidence for TPO-R as a key regulator of megakaryopoiesis is the fact that exposure of CD34<sup>+</sup> cells to synthetic oligonucleotides antisense to TPO-R RNA significantly inhibits the appearance of megakaryocyte colonies without affecting erythroid or myeloid colony formation. Some workers postulate that the receptor functions as a homodimer, similar to the situation with the receptors for G-CSF and erythropoietin.

The slow recovery of platelet levels in patients suffering from thrombocytopenia is a serious problem, and has lent urgency to the search for a blood growth factor agonist able to accelerate platelet regeneration.

It would be desirable to provide compounds which allow for the treatment of thrombocytopenia by acting as a TPO mimetic.

As disclosed herein it has unexpectedly been discovered that certain cyclam derivatives are effective as agonists of the TPO receptor, they are potent TPO mimetics.

#### SUMMARY OF THE INVENTION

The present invention involves novel compounds represented by Formulas (I), and (II) hereinbelow, their use as CXCR-4 receptor antagonists and their use as agonist of the TPO receptor.

The present invention further provides methods for antagonizing CXCR-4 receptors in an animal, including humans, which comprises administering to a subject in need of treatment an effective amount of a compound of Formula (I), and (II) as indicated hereinbelow.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented TPO mimetic - CXCR-4 receptor antagonist compounds.

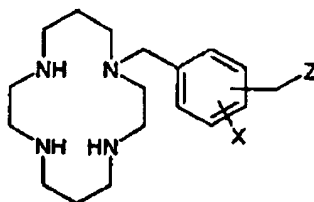
Included in the present invention are pharmaceutical compositions comprising a pharmaceutical carrier and compounds useful in the methods of the invention.

Also included in the present invention are methods of co-administering the presently invented TPO mimetic - CXCR-4 receptor antagonist compounds with further active ingredients.

#### DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present methods are selected from Formulas (I), and (II) hereinbelow.

Compounds of formula (I) have the following structure:



Formula (I)

wherein:

- the  $-\text{CH}_2\text{-Z}$  substituent is meta or para to the tetraazacyclotetradecane substituent;
- 5  $\text{Z}$  represents a nitrogen-linked heteroaryl, a substituted nitrogen-linked heteroaryl, a cyclic amine moiety, a substituted cyclic amine moiety, or  $\text{NY}^1\text{Y}^2$  where  $\text{Y}^1$  and  $\text{Y}^2$  are each independently selected from hydrogen, alkyl, substituted alkyl,  $\text{C}_3\text{-C}_{12}$ aryl, substituted  $\text{C}_3\text{-C}_{12}$ aryl, cycloalkyl, and substituted cycloalkyl; and
- 10  $\text{X}$  is selected from the group consisting of hydrogen, alkyl,  $\text{C}_3\text{-C}_{12}$ aryl, substituted  $\text{C}_3\text{-C}_{12}$ aryl, amino, alkylamino, nitro, hydroxy, alkoxy, halogen, carboxyl and carboxamido; and

pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

- 15 Preferred among the presently invented Formula (I) compounds are those in which the nitrogen-linked heteroaryl is selected from: benzimidazole, substituted benzimidazole, phenothiazine, substituted phenothiazine.

Particularly preferred among the presently invented Formula (I) compounds are those in which the nitrogen-linked heteroaryl is a substituted benzimidazole.

- 20 Preferred among the presently invented Formula (I) compounds are those in which cyclic amine moiety is selected from: piperazine, piperidine, azacycloheptane, diazacycloheptane, morpholine, azacyclotridecane, 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien, 1,4,7-trioxa-10-azacyclododecane, 1,4,7,10-tetraoxa-13-azacyclopentadecane, 1,4,8,11-tetraazacyclotetradecane, and diazacyclooctane.

- 25 Particularly preferred among the presently invented Formula (I) compounds are those in which cyclic amine moiety is selected from: 1,4-diazacycloheptane, azacyclotridecane, 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien, 1,4,8,11-tetraazacyclotetradecane, and 1,5-diazacyclooctane.

- 30 Preferred among the presently invented Formula (I) compounds are those in which  $\text{C}_3\text{-C}_{12}$ aryl, when representing  $\text{Y}^1$  and/or  $\text{Y}^2$ , is independently selected from: phenyl, quinoline, thiazole, pyrazole and pyridine.

Particularly preferred among the presently invented Formula (I) compounds are those in which C<sub>3</sub>-C<sub>12</sub>aryl, when representing Y<sup>1</sup> and/or Y<sup>2</sup> is independently selected from: phenyl and pyrazole.

Preferred among the presently invented Formula (I) compounds are those in which  
5 X is selected from: hydrogen, nitro and halogen.

By the term "heteroaryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and containing one to three heteroatoms; provided that one of the heteroatoms is nitrogen and provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms.

10 Examples of heteroaryl as used herein include: benzimidazole and phenothiazine.

By the term "cyclic amine moiety" as used herein, unless otherwise defined, is meant a nitrogen-linked, non-aromatic, cyclic or polycyclic ring system containing from about 5 to 24 atoms; of which 1 to 4 are nitrogen atoms and 0 to 4 are oxygen atoms, which heteroatoms being separated by 2 or more carbon atoms, wherein the moiety  
15 comprises 0 to 2 fused aromatic rings.

Examples of cyclic amine moiety as used herein include: piperazine, piperidine, azacycloheptane, diazacycloheptane, morpholine, azacyclotridecane, 5,6,14,15-dibenzo-1,4-dioxa-8,12-diazacyclopentadeca-5,14-dien, 1,4,7-trioxa-10-azacyclododecane, 1,4,7,10-tetraoxa-13-azacyclopentadecane, 1,4,8,11-tetraazacyclotetradecane, and 1,5-diazacyclooctane.  
20

By the term "C<sub>3</sub>-C<sub>12</sub>aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 3 to 12 carbon atoms and optionally containing one to three heteroatoms; provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and provided that when the number of  
25 carbon atoms is 4 the aromatic ring contains at least one heteroatom.

Examples of C<sub>3</sub>-C<sub>12</sub>aryl as used herein include: phenyl, benzimidazole, phenothiazine, quinoline, thiazole, pyrazole, pyridine, pyrimidine, naphthyl, 3,4-methylenedioxyphenyl and biphenyl.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

30 By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C<sub>3</sub>-C<sub>12</sub>.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein  
35 include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl and cyclopentyl.

By the term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: guanidino, hydroxyalkyl, alkoxy, acyloxy, alkyl, pyridyl, pyrimidyl, amino, alkylamino, dialkylamino, [(1,4,8,11,-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl], 3,4-methylenedioxyphenylmethyl, phenylalkyl, phenylmethyl, alkylphenyl, halogen substituted phenyl, dihalogen halogen substituted phenyl, thiazole, guanidinothiazole, thiophene, acetyl, N-acylamino, hydroxy, furan, phenyl,  $-(CH_2)_gC(O)OR^6$ ,  $-S(O)_nR^7$ , nitro, cyano, halogen, trifluoromethyl and protected -OH, where g is 0-6,  $R^6$  is hydrogen or alkyl, n is 0-2, and  $R^7$  is hydrogen or alkyl.

By the term "protected hydroxy" or "protected -OH" as used herein, is meant the alcoholic or carboxylic-OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Compounds containing protected hydroxy groups may also be useful as intermediates in the preparation of the pharmaceutically active compounds of the invention.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including -OCH<sub>3</sub> and -OC(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -OC(O)CH<sub>3</sub>, -OC(O)CH(CH<sub>3</sub>)<sub>2</sub> and -OC(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>.

By the term "N-acylamino" as used herein is meant -N(H)C(O)alkyl, where alkyl is as described herein. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH<sub>3</sub>, -N(H)C(O)CH(CH<sub>3</sub>)<sub>2</sub> and -N(H)C(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain having C<sub>1</sub>-C<sub>12</sub> carbon atoms. Examples of alkyl substituents as used herein include: -CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub> and -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>3</sub>, -CH=CH<sub>2</sub>.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic or therapeutic therapy.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

Compound represented by formula (II) have the following structure:

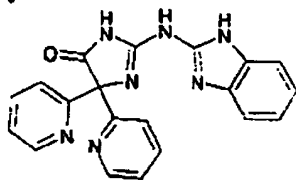


Formula (II)

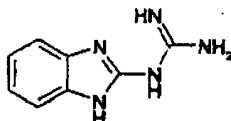
wherein,



Y' represents a moiety selected from



and



wherein the Y' moiety can be optionally substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen and carboxy; and

A represents an X'-substituted aryl or heteroaryl ring wherein X' is selected from the group consisting of hydrogen, alkyl, aryl, amino, alkylamino, nitro, hydroxy, alkoxy, halogen, carboxyl, and carboxamido;

provided that the YCH<sub>2</sub> groups are arranged meta or para to each other.

Preferred compounds, having formula (I), useful in the present invention are selected from the group consisting of:

1-[4-(4-Acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

1-[4-(Azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1-Piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1-Morpholinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

- 1-[4-(1,4,7-Trioxa-10-azacyclododecan-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(1,4,10-Trioxa-7,13-diazacyclopentadecan-7-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-[4-(2-Pyridyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-[4-(2-Pyrimidyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 10 1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(1-Piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 15 1,4-Bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride;
- 1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-{Bis[2-(diethylamino)ethyl]aminomethyl}phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride;
- 20 1-[4-[[2-(2-Aminoethyl)(3-aminopropyl)amino]methyl]phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride;
- 1-[4-[Di-(2-pyridyl)aminomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[4-(2-Thiazolylaminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(2-aminobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;

- 1-[4-(N-{3-(methylamino)propyl}-N-methylaminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(N-{3,4-methylenedioxyphenylmethyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(N-{3,5-difluorophenylmethyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 20 1-[3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[3-(N-{6-methyl-2-nitrophenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(N-{1-methyl-3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{3-(2-furyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[3-(N-{1-methyl-3-phenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane;
- 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane;
- 1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 20 1-[3-(N-{3-(4-*t*-butylphenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.
- 25 More preferred compounds of the present invention are selected from the group consisting of:
- 1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(Azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[4-(1-Piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;  
1-[4-(1,4,10-Trioxa-7,13-diazacyclopentadecan-7-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 5 1-[4-[4-(2-Pyridyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;  
1-[4-[4-(2-Pyrimidyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;  
1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1,4-Bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride;  
1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 15 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;  
1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;  
1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 20 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;  
1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;  
1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;  
1-[3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;  
1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes
- 20 thereof.

The most preferred compounds included in the present invention are selected from the group consisting of:

- 1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 25 1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane
- 30 pentahydrochloride;
- 1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and
- 15 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

Preferred compounds of formula (II) are selected from the group consisting of:

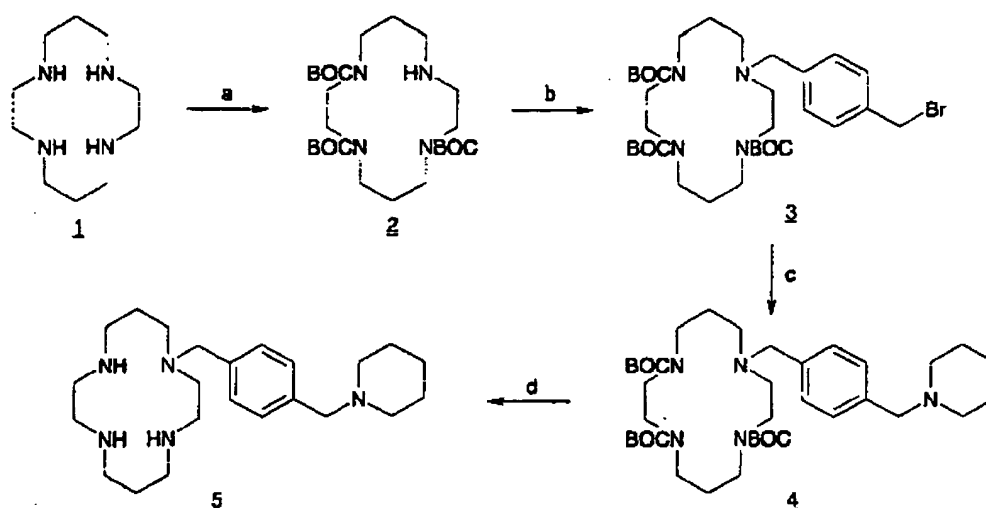
- 20 1,4-Bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]benzene bis-trifluoroacetic acid salt;
- 2,6-Bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]pyridine bis-trifluoroacetic acid salt; and
- 1,4-Bis[[1-(2-Benzimidazolyl)-1-guanidino]methyl]benzene;
- 25 or further pharmaceutically acceptable salts, hydrates, solvates, esters or metal complexes thereof.

- Also included in the present invention are pharmaceutically acceptable salts and complexes. Preferred are the zinc, copper, nickel, cobalt and rhodium complexes, hydrochloride, hydrobromide and trifluoroacetate salts. The compounds of the present
- 30 invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

The compounds of Formulas (I) and (II) are prepared as shown in Schemes I to IV below wherein the pendent substituents (X, Z, A, Y', Y<sup>1</sup>, Y<sup>2</sup> and X') are as defined in formulas 1 and 2 and provided that the pendent substituents do not include any such substituents that render inoperative the processes of Schemes I the IV. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

Compounds of formula I where X represents hydrogen are prepared by methods analogous to that shown in scheme 1.

10

Scheme 1

a) BOC<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>; b) α,α'-dibromo-*p*-xylene, K<sub>2</sub>CO<sub>3</sub>, MeCN, 60°C; c) piperidine, K<sub>2</sub>CO<sub>3</sub>, MeCN, 60°C; d) HCl, dioxane, CH<sub>2</sub>Cl<sub>2</sub>.

Compound 1, available commercially, is protected as its tri-*tert*-butylcarbamate derivative 2, which is alkylated on the free nitrogen to give compound 3. The benzylic bromide is displaced with the appropriate N nucleophile to give the protected precursor 4, which is deprotected with acid to furnish the final compound 5.

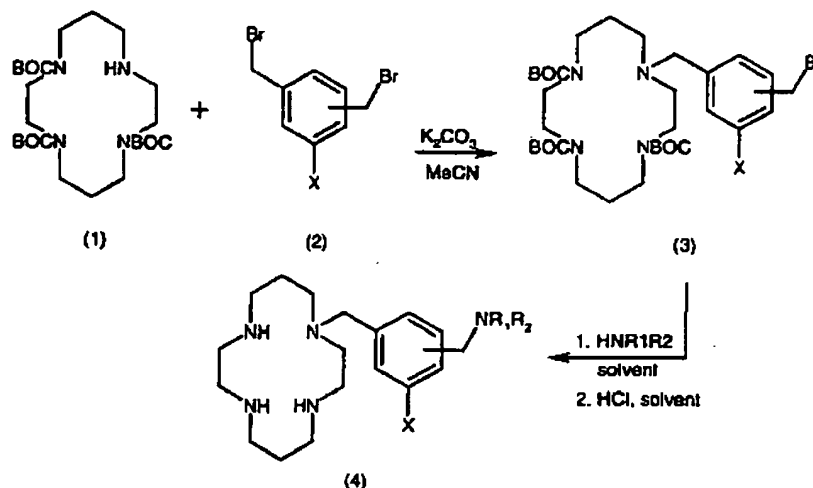
Compounds where the -CH<sub>2</sub>-Z substituent is in the "meta" position can be readily made by the skilled worker, using commercially available starting materials or using materials readily made from commercially available materials by analogous methods.

Compounds of formula I where X is other than hydrogen are prepared by methods analogous to that shown in scheme 2. Further, compounds of formula I where Z represents NY<sup>1</sup>Y<sup>2</sup> are prepared by methods analogous to that shown in scheme 2.

25

Scheme 2





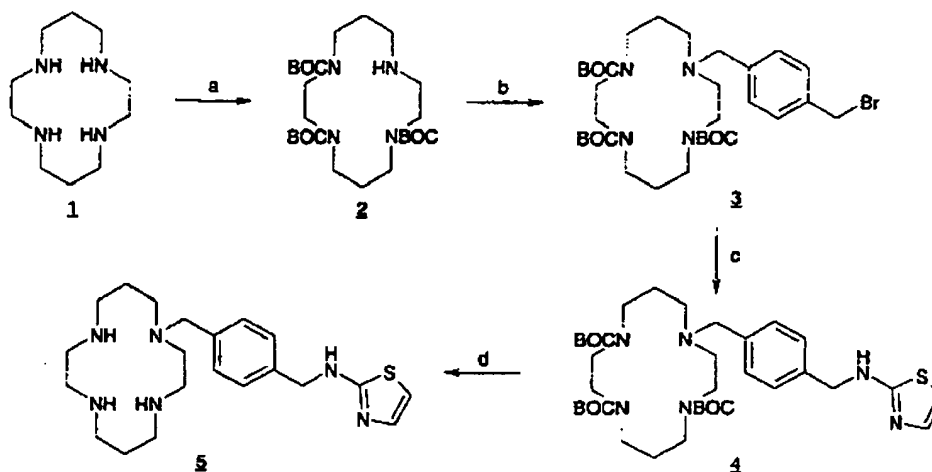
Compound **1**, available commercially, is alkylated with dibromides **2**, prepared by literature methods, in a suitable solvent in the presence of potassium carbonate to give the mono-bromide **3**. **3** was heated with amines  $R_1R_2NH$  (as used in this Scheme,  $R_1R_2$  is  $Y^1$   $Y^2$  of formula **1**) in a suitable solvent with or without the addition of a base to give intermediates which were deprotected with HCl to furnish the final compounds **4**.

Compounds where the  $-CH_2-Z$  substituent is in the "meta" position can be readily made by the skilled worker, using commercially available starting materials or using materials readily made from commercially available materials by analogous methods.

10

Compounds of formula **I** where  $Z$  represents  $NY^1Y^2$  are also prepared by methods analogous to that shown in scheme 3.

Scheme 3



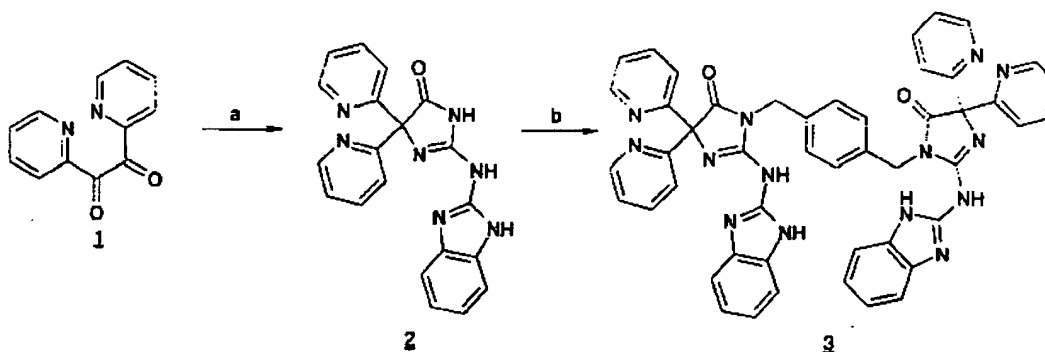
15 a)  $BOC_2O$ ,  $CH_2Cl_2$ ; b)  $\alpha,\alpha'$ -dibromo-*p*-xylene,  $K_2CO_3$ , MeCN,  $60^\circ C$ ; c) 2-aminothiazole,  $K_2CO_3$ , MeCN,  $60^\circ C$ ; d) HCl, dioxane,  $CH_2Cl_2$ .

Compound 1, available commercially, is protected as its tri-*tert*-butylcarbamate derivative 2, which is alkylated on the free nitrogen to give compound 3. The benzylic bromide is displaced with the appropriate N nucleophile to give the protected precursor 4, which is deprotected with acid to furnish the final compound 5.

- 5        Compounds where the -CH<sub>2</sub>-Z substituent is in the "meta" position can be readily made by the skilled worker, using commercially available starting materials or using materials readily made from commercially available materials by analogous methods.

10        Compounds of formula (II) are prepared by methods analogous to that shown in scheme 4.

Scheme 4



- 15        a) 2-Guanidinobenzimidazole, NaOH, rt; b)  $\alpha, \alpha'$ -dibromo-p-xylene, DMF, rt Compound 1, available commercially, condenses with 2-guanidinobenzimidazole to give the rearranged product 2, which is converted to its sodium salt and alkylated regioselectively with a bis-electrophile to give compound 3.

20        With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) and (II) is accomplished by methods analogous to those above and to those described in the Experimental section.

Pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes of the presently invented compounds are readily prepared by those of skill in the art using readily available starting materials.

- 25        In order to use a compound of the Formula (I) or (II) or a pharmaceutically acceptable salt, hydrate, solvate, ester or metal complex thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Because the present compounds have been found to act as CXCR-4 receptor antagonist they are useful for the treatment of diseases including but not limited to bacterial, fungal and protozoan infections, pain, thrombocytopenia, cancer, diabetes, obesity, anorexia, bulimia, asthma, allergies, Parkinson's disease, acute heart failure, hypotension, hypertension, neural damage, atherosclerosis, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers, benign prostatic hypertrophy, migraine, angiogenesis, vomiting, psychotic and neurological disorders (e.g. anxiety, schizophrenia, manic depression, depression, delirium, dementia, mental retardation) and dyskinesias (Huntington's disease and Gilles de la Tourette's syndrome), viral infections, such as HIV infection in patients having clinical signs of AIDS and for the treatment of asymptomatic HIV-infected subjects. The present compounds are also useful for the treatment of an injured or severed spinal cord and other injury-related disease states.

The treatment of thrombocytopenia, as described herein, is accomplished by enhancing the production of platelets.

By the term "co-administering" and derivatives thereof as used herein when directed to the TPO mimetic aspect of this invention is meant either simultaneous administration or any manner of separate sequential administration of a TPO mimetic compound, as described herein, and a further active ingredient or ingredients, known to treat thrombocytopenia, including chemotherapy-induced thrombocytopenia and bone marrow transplantation and other conditions with depressed platelet production. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Because the compounds of the present invention have been found to be active as TPO mimetics they exhibit therapeutic utility in treating thrombocytopenia and other conditions with depressed platelet production.

In determining potency as TPO mimetics, the following assays were employed:

Luciferase Assay

Compounds of the present invention were tested for potency as mimetics of the TPO receptor in a Luciferase assay such as described in Lamb, et al., Nucleic Acids Research 23: 3283-3289 (1995) and Seidel, et al., Proc. Natl. Acad. Sci. USA 92: 3041-3045 (1995) by substituting a TPO-responsive BaF3 cell line (Vigon et al. Proc. Natl. Acad. Sci. USA 1992, 89, 5640-5644) for the HepG2 cells utilized therein. The murine BaF3 cells express TPO receptors and closely match the pattern of STAT (signal

transducers and activators of transcription) activation observed in primary murine and human bone marrow cells in response to TPO.

Some of the most preferred compounds of this invention were also active in an in vitro proliferation assay using the human UT-7/TPO leukemic megakaryoblastic cell line (Komatsu, N. et al., Blood, 1996, 87, 4552-4560). UT-7/TPO cells express TPO-R and are absolutely dependent on the presence of TPO for growth and survival. Likewise, some of the most preferred compounds of this invention were also positive in stimulating the maturation of megakaryocytes from human bone marrow cells. In this assay, purified human CD34+ progenitor cells were incubated in liquid culture with test compounds for 10 days and the number of cells expressing the transmembrane glycoprotein CD41 (gpIIb), a megakaryocytic marker, was then measured by flow cytometry (see Cwirla, S. E. et al Science, 1997, 276, 1696-1699).

The pharmaceutically active compounds within the scope of this invention are useful as TPO mimetics in mammals, including humans, in need thereof.

Some of the preferred compounds within the scope of the invention showed activation from about 5% to 100% of control (control is the maximal response to TPO) at a concentration of 0.1-30  $\mu$ M in the luciferase assay. The preferred compounds of the invention also promoted the proliferation of UT-7/TPO cells at a concentration of 0.1 to 30  $\mu$ M. The preferred compounds of the invention also showed activity in the CD41 megakaryocytic assay at a concentration of 0.1 to 30  $\mu$ M.

The activity of the compound of Example 46 in the luciferase assay is: 86% of maximal TPO effect with an EC50 of 2.7  $\mu$ M.

One aspect of the present invention therefor provides a method of treating thrombocytopenia and other conditions with depressed platelet production, which comprises administering a compound of Formula (I) or (II), as described above, in a quantity effective to enhance platelet production. The compounds of Formulas (I) and (II) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as TPO mimetics. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The present invention therefor provides a method of treating thrombocytopenia and other conditions with depressed platelet production, which comprises administering a compound of Formula (I) or (II), as described above, in a quantity effective to enhance platelet production. The compounds of Formulas (I) and (II) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as TPO mimetics. The drug may be administered to a patient in need thereof by any

conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of a pharmaceutically active compound of this invention, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular active in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing TPO mimetic activity in mammals, including humans, comprises administering to a subject in need of such activity an effective TPO mimetic amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use as a TPO mimetic.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use in enhancing platelet production.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use in treating thrombocytopenia.

The invention also provides for a pharmaceutical composition for use as a TPO mimetic which comprises a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier.

The invention also provides for a pharmaceutical composition for use in the treatment of thrombocytopenia which comprises a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier.

5 The invention also provides for a pharmaceutical composition for use in enhancing platelet production which comprises a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier.

10 In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to antagonize the CXCR-4 receptor or which exhibit a therapeutic effect on a disease state that is treatable with a CXCR-4 receptor antagonist; or such as other compounds known to treat thrombocytopenia, including chemotherapy-induced thrombocytopenia and bone marrow transplantation and other conditions with depressed platelet production, or compounds known to have utility when used in combination with a TPO mimetic.

15 No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The activity of the compounds of Formula (I) and (II) as antagonists of the CXCR-4 receptor are demonstrated by the following test.

CXCR-4/SDF-1 Assay Protocol

20 Assay plates were seeded with RBL transfected with the SDF-1 receptor. Dye loading buffer (EMEM w/Earl's salts w/ L-glutamine with 1X Sulphinpyrozone and 10% BSA, 100 uL) was added to each well, and the plate incubated for 90 minutes at 37°C. The dye loading buffer was aspirated from the plates. Hydrolysis buffer (EMEM w/Earl's salts w/ L-glutamine with 1X Sulphinpyrozone, 100uL) was added to each well, and the plate incubated for 10 minutes at 37°C. The cells were washed 3 times with wash buffer (1X  
25 Krebs Ringer, 15 mM HEPES, 1mM MgCl, 1 mM CaCl with 1X Sulphinpyrozone and 0.10% gelatin), then wash buffer was dispensed to each well (100uL/well). The plate was incubated for 10 minutes at 37°C, then placed in FLIPR™ (Molecular Devices). Test compounds in gelatin buffer (1X Krebs Ringer, 15 mM HEPES, 1mM MgCl, 1 mM CaCl with 0.10% gelatin, 50uL) were preincubated with cells for 3 minutes, then ligand (SDF-  
30 1alpha/PBSF, 15nM final concentration) was added. The plate was incubated for 2 minutes while continually reading.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following  
35 Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

### Experimental Details

#### Example 1

##### Preparation of 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

*a,a'*-Dibromo-*p*-xylene (36.0 g, 136 mmol) was stirred at 60°C in acetonitrile (500 mL) until it dissolved. Potassium carbonate (3.5 g, 25.3 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (6.0 g, 11.98 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2% methanol/dichloromethane) to afford the title compound as a foam (7.4 g, 90 %). MS (ES+) *m/e* 683 and 685 [M+H]<sup>+</sup>.

b) 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (326 mg, 0.477 mmol), 1-acetylpiperazine (95 mg, 0.741 mmol) and anhydrous potassium carbonate (350 mg, 2.53 mmol) in acetonitrile (30 mL) was vigorously stirred together at 50°C for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-3% methanol/dichloromethane) to give the title compound as an oil (300 mg, 86%). MS (ES+) *m/e* 731 [M+H]<sup>+</sup>.

c) 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

To a solution of 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (175 mg, 0.239 mmol) in 1,4-dioxane (1.0 mL) was added a solution of 4M hydrogen chloride in 1,4-dioxane (1.0 mL). The mixture was stood for 2 hours, the white solid collected and washed successively with 1,4-dioxane, diethyl ether and hexane.

The hygroscopic solid was dried *in vacuo* (80°C) to give the title compound (35 mg, 34%). MS (ES+) *m/e* 431 [M+H]<sup>+</sup>

#### Example 2

Preparation of 1-[4-(1,4-diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting homopiperazine for 1-acetylpiperazine, the title compound was prepared (27% overall). <sup>1</sup>H NMR (300MHz, d3-MeOD/D<sub>2</sub>O) δ 7.67 (d, 2H), 7.50 (d, 2H), 4.52 (s, 2H), 3.98 (s, 2H), 3.90 (s, 2H), 3.62 (m, 2H), 3.53-3.20 (m, 8H), 3.15 (m, 2H), 2.95 (m, 4H), 2.35 (m, 2H), 2.19 (m, 4H), 2.09 (m, 2H), 1.26 (m, 4H).

Example 3

Preparation of 1-[4-(azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting hexamethyleneimine for 1-acetylpiperazine, the title compound was prepared (45% overall). MS (ES+) m/e 402 [M+H]<sup>+</sup>.

Example 4

Preparation of 1-[4-(1-piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting piperidine for 1-acetylpiperazine, the title compound was prepared (75% overall). MS (ES+) m/e 388 [M+H]<sup>+</sup>.

Example 5

Preparation of 1-[4-(1-morpholinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting morpholine for 1-acetylpiperazine, the title compound was prepared (60% overall). <sup>1</sup>H NMR (300MHz, D<sub>2</sub>O) δ 7.7-7.5 (m, 4H), 4.5 (s, 2H), 4.1 (m, 4H), 3.8 (br m, 2H), 3.6-3.0 (br m, 16H), 2.2 (br s, 4H), 1.2 (s, 4H).

Example 6

Preparation of 1-[4-(azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting azacyclotridecane for 1-acetylpiperazine, the title compound was prepared (13% overall). MS (ES+) m/e 522 [M+H+HCl]<sup>+</sup>.

Example 7



Preparation of 1-[4-(5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-diene for 1-acetylpiperazine, the title compound was prepared (42% overall). <sup>1</sup>H NMR (300MHz, d<sub>6</sub>-DMSO, D<sub>2</sub>O) δ 7.90-6.95(m, 12H), 4.7-4.1 (m, 14H), 3.5 (s, 2H), 3.45 (s, 2H), 3.5-3.0 (br m, 6H), 2.85-2.30 (br m, 2H), 2.3-2.0 (br m, 6H), 1.2 (br s, 6H.).

Example 8

Preparation of 1-[4-(1,4,7-trioxo-10-azacyclododecan-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-aza-12-crown for 1-acetylpiperazine, the title compound was prepared (86% overall). MS (ES+) m/e 478 [M+H]<sup>+</sup>.

Example 9

Preparation of 1-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-aza-15-crown-5 for 1-acetylpiperazine, the title compound was prepared (50% overall). MS (ES+) m/e 522 [M+H]<sup>+</sup>.

Example 10

Preparation of 1-[4-(1,4,10-trioxo-7,13-diazacyclopentadecan-7-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1,4,10-trioxo-7,13-diaza-cyclopentadecane for 1-acetylpiperazine, the title compound was prepared (21% overall). MS (ES+) m/e 261 [M+2H]<sup>2+</sup>, 557.

Example 11

Preparation of 1-[4-[4-(2-pyridyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-(2-pyridyl)piperazine for 1-acetylpiperazine, the title compound was prepared (24% overall). MS (ES+) m/e 466 [M+H]<sup>+</sup>, 502.

Example 12

Preparation of 1-[4-[4-(2-pyrimidyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-(2-pyrimidyl)piperazine for 1-acetylpiperazine, the title compound was prepared (25% overall). MS (ES+)  $m/e$  467  $[M+H]^+$ , 503.

#### Example 13

##### 5 Preparation of 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

10 A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (293 mg, 0.429 mmol) and 2-guanidinobenzimidazole (225 mg, 1.28 mmol) in acetonitrile (5 mL) was stirred and heated under reflux for 30 min. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-5 % methanol/dichloromethane) to give the title compound as a yellow gum, (115 mg, 34%). MS (ES+)  $m/e$  778  $[M+H]^+$ .

15 b) 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

To a solution of 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (115 mg, 0.148 mmol) in 1,4-dioxane (2.0 mL) was added a 4M solution of hydrogen  
20 chloride in 1,4-dioxane (1.5 mL). The mixture was stood overnight, the red solid collected and washed successively with 1, 4,-dioxane, diethyl ether and hexane. The hygroscopic solid was dried *in vacuo* (80°C) to give the title compound (72 mg, 73%). MS (ES+)  $m/e$  478  $[M+H]^+$ .

#### Example 14

##### 25 Preparation of 1-[4-(1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting piperazine for 1-acetylpiperazine, the title compound was prepared (32% overall). MS (ES+)  $m/e$  389  $[M+H]^+$ .

#### 30 Example 15

##### Preparation of 1,4-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride

a) 1,4-bis-[4-[4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-ylmethyl]phenylmethyl]piperazine

A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (287 mg, 0.449 mmol), piperazine (92 mg, 1.07 mmol) and anhydrous potassium carbonate (100 mg, 0.724 mmol) in acetonitrile (5 mL) was vigorously stirred together at 50°C for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-5 % methanol/dichloromethane) to give the title compound as an oil, (114 mg, 21%).

MS *m/e* 646 [M+2H]<sup>2+</sup>.

b) 1,4-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride

Following the procedure of Example 1(c), except substituting 1,4-bis-[4-(1,4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine for 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane, the title compound was prepared (56%). MS (ES+) *m/e* 346 [M+2H]<sup>2+</sup>.

#### Example 16

Preparation of 1-[4-(1,5-diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1,5-diazacyclooctane dihydrobromide (G. Ewin *et al.*, *J. Chem. Res., Synop.*, 1985, 11, 334) for 1-acetylpiperazine, the title compound was prepared (6% overall). <sup>1</sup>H NMR (300MHz, d6-DMSO/D<sub>2</sub>O) δ 7.74 (s, 4H), 4.43 (br s, 4H), 3.6-3.0 (br m, 20H), 2.21 (br m, 12H).

#### Example 17

1-[4-(bis[2-(diethylamino)ethylaminomethyl]phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride

a) 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

*o,o'*-Dibromo-*p*-xylene (36.0 g, 136 mmol) was stirred at 60°C in acetonitrile (500 mL) until it dissolved. Potassium carbonate (3.5 g, 25.3 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butyloxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (6.0 g, 11.98 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2%

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<p>(54) Title: CXCR-4 RECEPTOR ANTAGONISTS - THROMBOPOIETIN MIMETICS (57) Abstract  Invented are substituted cyclam derivatives, pharmaceutical compositions containing these compounds, the use of these compounds as CXCR-4 receptor antagonists and to use of these compounds as thrombopoietin (TPO) mimetics.</p>		

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## CXCR-4 RECEPTOR ANTAGONISTS - THROMBOPOIETIN MIMETICS

## FIELD OF THE INVENTION

The present invention relates to cyclam derivatives, pharmaceutical compositions containing these compounds, the use of these compounds as CXCR-4 receptor antagonists and to use of these compounds as promoters of thrombopoiesis and megakaryocytopoiesis.

## BACKGROUND OF THE INVENTION

The CXCR-4 receptor, originally known as LESTR/fusin, was shown to be the receptor for the  $\alpha$  or CXC chemokine stromal cell-derived factor-1 (SDF-1) in 1996 and renamed at this time. SDF-1 appears to be specific for CXCR-4 and mediates its chemotactic effects via this receptor. The CXCR-4 receptor is widely expressed in a variety of cell types and is implicated in a range of inflammatory responses mediated by SDF-1.

The widespread distribution of the receptor leads to its involvement in a number of disease areas including bacterial, fungal and protozoan infections, pain, cancer, diabetes, obesity, anorexia, bulimia, asthma, allergies, Parkinson's disease, acute heart failure, hypotension, hypertension, atherosclerosis, disease states involving angiogenesis, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers, benign prostatic hypertrophy, migraine, vomiting, psychotic and neurological disorders (e.g. anxiety, schizophrenia, manic depression, depression, delirium, dementia, mental retardation) and dyskinesias (Huntington's disease and Gilles de la Tourette's syndrome), injured or severed spinal cord and other injury related disease states.

In addition, CXCR-4 has been identified as the co-receptor used by T-tropic HIV-1 viral strains to infect cells, and antagonists of the receptor may therefore be useful in the treatment of late stage HIV infection and AIDS.

Based on the foregoing, CXCR-4 receptor antagonists offer a unique approach toward decreasing the pathophysiology associated with the aforementioned diseases.

As disclosed herein it has unexpectedly been discovered that certain cyclam derivatives are effective as CXCR-4 receptor antagonists.

Megakaryocytes are bone marrow-derived cells, which are responsible for producing circulating blood platelets. Although comprising <0.25% of the bone marrow cells in most species, they have >10 times the volume of typical marrow cells. See Kuter et al. Proc. Natl. Acad. Sci. USA 91: 11104-11108 (1994). Megakaryocytes undergo a process known as endomitosis whereby they replicate their nuclei but fail to undergo cell division and thereby give rise to polyploid cells. In response to a decreased platelet count, the endomitotic rate increases, higher ploidy megakaryocytes are formed, and the number of megakaryocytes may increase up to 3-fold. See Harker J. Clin. Invest. 47: 458-465 (1968). In contrast, in response to an

elevated platelet count, the endomitotic rate decreases. lower ploidy megakaryocytes are formed, and the number of megakaryocytes may decrease by 50%.

The exact physiological feedback mechanism by which the mass of circulating platelets regulates the endomitotic rate and number of bone marrow megakaryocytes is not known. The circulating thrombopoietic factor involved in mediating this feedback loop is now thought to be thrombopoietin (TPO). More specifically, TPO has been shown to be the main humoral regulator in situations involving thrombocytopenia. See, e.g., Metcalf *Nature* 369:519-520 (1994). TPO has been shown in several studies to increase platelet counts, increase platelet size, and increase isotope incorporation into platelets of recipient animals. Specifically, TPO is thought to affect megakaryocytopoiesis in several ways: (1) it produces increases in megakaryocyte size and number; (2) it produces an increase in DNA content, in the form of polyploidy, in megakaryocytes; (3) it increases megakaryocyte endomitosis; (4) it produces increased maturation of megakaryocytes; and (5) it produces an increase in the percentage of precursor cells, in the form of small acetylcholinesterase-positive cells, in the bone marrow.

Because platelets (thrombocytes) are necessary for blood clotting and when their numbers are very low a patient is at risk of death from catastrophic hemorrhage, TPO has potential useful application in both the diagnosis and the treatment of various hematological disorders, for example, diseases primarily due to platelet defects. Ongoing clinical trials with TPO have indicated that TPO can be administered safely to patients. In addition, recent studies have provided a basis for the projection of efficacy of TPO therapy in the treatment of thrombocytopenia, and particularly thrombocytopenia resulting from chemotherapy, radiation therapy, or bone marrow transplantation as treatment for cancer or lymphoma. See e.g., McDonald (1992) *Am. J. Ped. Hematology/Oncology* 14: 8-21 (1992).

The gene encoding TPO has been cloned and characterized. See Kuter et al., *Proc. Natl. Acad. Sci. USA* 91: 11104-11108 (1994); Barley et al., *Cell* 77: 1117-1124 (1994); Kaushansky et al., *Nature* 369:568-571 (1994); Wendling et al., *Nature* 369: 571-574 (1994); and Sauvage et al., *Nature* 369: 533-538 (1994). Thrombopoietin is a glycoprotein with two distinct regions separated by a potential Arg-Arg cleavage site. The amino-terminal region is highly conserved in man and mouse, and has some homology with erythropoietin and interferon-alpha and interferon-beta. The carboxy-terminal region shows wide species divergence.

The DNA sequences and encoded peptide sequences for human TPO receptor (TPO-R; also known as c-mpl) have been described. See, Vigon et al. *Proc. Natl. Acad. Sci. USA* 89: 5640-5644 (1992). TPO-R is a member of the haematopoietin growth factor receptor family, a family characterized by a common structural design of the extracellular domain, including for conserved C residues in the N-terminal portion and a WSXWS motif close to the transmembrane region. See Bazan *Proc. Natl. Acad. Sci. USA* 87: 6934-6938 (1990). Evidence that this

receptor plays a functional role in hematopoiesis includes observations that its expression is restricted to spleen, bone marrow, or fetal liver in mice (see Souyri et al. Cell 63: 1137-1147 (1990)) and to megakaryocytes, platelets, and CD34<sup>+</sup> cells in humans (see Methia et al. Blood 82: 1395-1401 (1993)). Further evidence for TPO-R as a key regulator of megakaryopoiesis is the fact that exposure of CD34<sup>+</sup> cells to synthetic oligonucleotides antisense to TPO-R RNA significantly inhibits the appearance of megakaryocyte colonies without affecting erythroid or myeloid colony formation. Some workers postulate that the receptor functions as a homodimer, similar to the situation with the receptors for G-CSF and erythropoietin.

The slow recovery of platelet levels in patients suffering from thrombocytopenia is a serious problem, and has lent urgency to the search for a blood growth factor agonist able to accelerate platelet regeneration.

It would be desirable to provide compounds which allow for the treatment of thrombocytopenia by acting as a TPO mimetic.

As disclosed herein it has unexpectedly been discovered that certain cyclam derivatives are effective as agonists of the TPO receptor, they are potent TPO mimetics.

#### SUMMARY OF THE INVENTION

The present invention involves novel compounds represented by Formulas (I), and (II) hereinbelow, their use as CXCR-4 receptor antagonists and their use as agonist of the TPO receptor.

The present invention further provides methods for antagonizing CXCR-4 receptors in an animal, including humans, which comprises administering to a subject in need of treatment an effective amount of a compound of Formula (I), and (II) as indicated hereinbelow.

In a further aspect of the invention there is provided novel processes and novel intermediates useful in preparing the presently invented TPO mimetic - CXCR-4 receptor antagonist compounds.

Included in the present invention are pharmaceutical compositions comprising a pharmaceutical carrier and compounds useful in the methods of the invention.

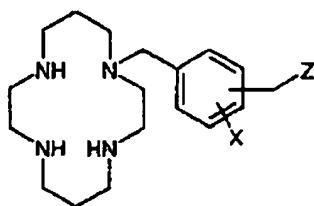
Also included in the present invention are methods of co-administering the presently invented TPO mimetic - CXCR-4 receptor antagonist compounds with further active ingredients.

#### DETAILED DESCRIPTION OF THE INVENTION

The compounds useful in the present methods are selected from Formulas (I), and (II) hereinbelow.

Compounds of formula (I) have the following structure:





Formula (I)

wherein:

the  $-CH_2-Z$  substituent is meta or para to the tetraazacyclotetradecane substituent;  
 5 Z represents a nitrogen-linked heteroaryl, a substituted nitrogen-linked heteroaryl, a cyclic amine moiety, a substituted cyclic amine moiety, or  $NY^1Y^2$  where  $Y^1$  and  $Y^2$  are each independently selected from hydrogen, alkyl, substituted alkyl,  $C_3-C_{12}$ aryl, substituted  $C_3-C_{12}$ aryl, cycloalkyl, and substituted cycloalkyl; and  
 X is selected from the group consisting of hydrogen, alkyl,  $C_3-C_{12}$ aryl, substituted  
 10  $C_3-C_{12}$ aryl, amino, alkylamino, nitro, hydroxy, alkoxy, halogen, carboxyl and carboxamido; and  
 pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

15 Preferred among the presently invented Formula (I) compounds are those in which the nitrogen-linked heteroaryl is selected from: benzimidazole, substituted benzimidazole, phenothiazine, substituted phenothiazine.

Particularly preferred among the presently invented Formula (I) compounds are those in which the nitrogen-linked heteroaryl is a substituted benzimidazole.

20 Preferred among the presently invented Formula (I) compounds are those in which cyclic amine moiety is selected from: piperazine, piperidine, azacycloheptane, diazacycloheptane, morpholine, azacyclotridecane, 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien, 1,4,7-trioxa-10-azacyclododecane, 1,4,7,10,-tetraoxa-13-azacyclopentadecane, 1,4,8,11-tetraazacyclotetradecane, and diazacyclooctane.

25 Particularly preferred among the presently invented Formula (I) compounds are those in which cyclic amine moiety is selected from: 1,4-diazacycloheptane, azacyclotridecane, 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien, 1,4,8,11-tetraazacyclotetradecane, and 1,5-diazacyclooctane.

Preferred among the presently invented Formula (I) compounds are those in which  
 30  $C_3-C_{12}$ aryl, when representing  $Y^1$  and/or  $Y^2$ , is independently selected from: phenyl, quinoline, thiazole, pyrazole and pyridine.

Particularly preferred among the presently invented Formula (I) compounds are those in which C<sub>3</sub>-C<sub>12</sub>aryl, when representing Y<sup>1</sup> and/or Y<sup>2</sup> is independently selected from: phenyl and pyrazole.

Preferred among the presently invented Formula (I) compounds are those in which  
5 X is selected from: hydrogen, nitro and halogen.

By the term "heteroaryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 3 to 16 carbon atoms and containing one to three heteroatoms; provided that one of the heteroatoms is nitrogen and provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms.

10 Examples of heteroaryl as used herein include: benzimidazole and phenothiazine.

By the term "cyclic amine moiety" as used herein, unless otherwise defined, is meant a nitrogen-linked, non-aromatic, cyclic or polycyclic ring system containing from about 5 to 24 atoms; of which 1 to 4 are nitrogen atoms and 0 to 4 are oxygen atoms, which heteroatoms being separated by 2 or more carbon atoms, wherein the moiety  
15 comprises 0 to 2 fused aromatic rings.

Examples of cyclic amine moiety as used herein include: piperazine, piperidine, azacycloheptane, diazacycloheptane, morpholine, azacyclotridecane, 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien, 1,4,7-trioxa-10-azacyclododecane, 1,4,7,10,-tetraoxa-13-azacyclopentadecane, 1,4,8,11-tetraazacyclotetradecane, and 1,5-  
20 diazacyclooctane.

By the term "C<sub>3</sub>-C<sub>12</sub>aryl" as used herein, unless otherwise defined, is meant a cyclic or polycyclic aromatic ring containing from 3 to 12 carbon atoms and optionally containing one to three heteroatoms; provided that when the number of carbon atoms is 3 the aromatic ring contains at least two heteroatoms and provided that when the number of  
25 carbon atoms is 4 the aromatic ring contains at least one heteroatom.

Examples of C<sub>3</sub>-C<sub>12</sub>aryl as used herein include: phenyl, benzimidazole, phenothiazine, quinoline, thiazole, pyrazole, pyridine, pyrimidine, naphthyl, 3,4-methylenedioxyphenyl and biphenyl.

By the term "heteroatom" as used herein is meant oxygen, nitrogen or sulfur.

30 By the term "halogen" as used herein is meant a substituent selected from bromide, iodide, chloride and fluoride.

The term "cycloalkyl" as used herein unless otherwise defined, is meant a nonaromatic, unsaturated or saturated, cyclic or polycyclic C<sub>3</sub>-C<sub>12</sub>.

Examples of cycloalkyl and substituted cycloalkyl substituents as used herein  
35 include: cyclohexyl, 4-hydroxy-cyclohexyl, 2-ethylcyclohexyl, propyl 4-methoxycyclohexyl, 4-methoxycyclohexyl, 4-carboxycyclohexyl and cyclopentyl.

By the term "substituted" as used herein, unless otherwise defined, is meant that the subject chemical moiety has one or more substituents selected from the group consisting of: guanidino, hydroxyalkyl, alkoxy, acyloxy, alkyl, pyridyl, pyrimidyl, amino, alkylamino, dialkylamino, [(1,4,8,11,-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl], 3,4-methylenedioxyphenylmethyl, phenylalkyl, phenylmethyl, alkylphenyl, halogen substituted phenyl, dihalogen halogen substituted phenyl, thiazole, guanidinothiazole, thiophene, acetyl, N-acylamino, hydroxy, furan, phenyl,  $-(CH_2)_gC(O)OR^6$ ,  $-S(O)_nR^7$ , nitro, cyano, halogen, trifluoromethyl and protected -OH, where g is 0-6,  $R^6$  is hydrogen or alkyl, n is 0-2, and  $R^7$  is hydrogen or alkyl.

By the term "protected hydroxy" or "protected -OH" as used herein, is meant the alcoholic or carboxylic-OH groups which can be protected by conventional blocking groups in the art as described in "Protective Groups In Organic Synthesis" by Theodora W. Greene, Wiley-Interscience, 1981, New York. Compounds containing protected hydroxy groups may also be useful as intermediates in the preparation of the pharmaceutically active compounds of the invention.

By the term "alkoxy" as used herein is meant -Oalkyl where alkyl is as described herein including -OCH<sub>3</sub> and -OC(CH<sub>3</sub>)<sub>2</sub>CH<sub>3</sub>.

By the term "acyloxy" as used herein is meant -OC(O)alkyl where alkyl is as described herein. Examples of acyloxy substituents as used herein include: -OC(O)CH<sub>3</sub>, -OC(O)CH(CH<sub>3</sub>)<sub>2</sub> and -OC(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>.

By the term "N-acylamino" as used herein is meant -N(H)C(O)alkyl, where alkyl is as described herein. Examples of N-acylamino substituents as used herein include: -N(H)C(O)CH<sub>3</sub>, -N(H)C(O)CH(CH<sub>3</sub>)<sub>2</sub> and -N(H)C(O)(CH<sub>2</sub>)<sub>3</sub>CH<sub>3</sub>.

By the term "alkyl" and derivatives thereof and in all carbon chains as used herein is meant a linear or branched, saturated or unsaturated hydrocarbon chain having C<sub>1</sub>-C<sub>12</sub> carbon atoms. Examples of alkyl substituents as used herein include: -CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>3</sub>, -CH(CH<sub>3</sub>)<sub>2</sub>, -C(CH<sub>3</sub>)<sub>3</sub>, -(CH<sub>2</sub>)<sub>3</sub>-CH<sub>3</sub>, -CH<sub>2</sub>-CH(CH<sub>3</sub>)<sub>2</sub> and -CH(CH<sub>3</sub>)-CH<sub>2</sub>-CH<sub>3</sub>, -CH=CH<sub>2</sub>.

By the term "treating" and derivatives thereof as used herein, is meant prophylactic or therapeutic therapy.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as though fully set forth.

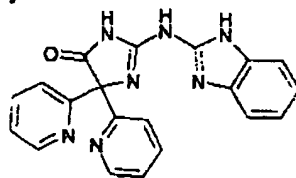
Compound represented by formula (II) have the following structure:



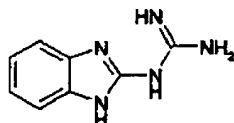
Formula (II)

wherein,

Y' represents a moiety selected from



and



wherein the Y' moiety can be optionally substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen and carboxy; and

A represents an X'-substituted aryl or heteroaryl ring wherein X' is selected from the group consisting of hydrogen, alkyl, aryl, amino, alkylamino, nitro, hydroxy, alkoxy, halogen, carboxyl, and carboxamido;

provided that the Y'CH<sub>2</sub> groups are arranged meta or para to each other.

Preferred compounds, having formula (I), useful in the present invention are selected from the group consisting of:

1-[4-(4-Acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

1-[4-(Azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1-Piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1-Morpholinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

- 1-[4-(1,4,7-Trioxa-10-azacyclododecan-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(1,4,10-Trioxa-7,13-diazacyclopentadecan-7-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-[4-(2-Pyridyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-[4-(2-Pyrimidyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 10 1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(1-Piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 15 1,4-Bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride;
- 1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-{Bis[2-(diethylamino)ethyl]aminomethyl}phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride;
- 20 1-[4-[[2-Aminoethyl)(3-aminopropyl)amino]methyl]phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride;
- 1-[4-[Di-(2-pyridyl)aminomethyl]phenylmethyl)-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[4-(2-Thiazolylaminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(2-aminobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;

- 1-[4-(N-{3-(methylamino)propyl}-N-methylaminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(N-{3,4-methylenedioxyphenylmethyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(N-{3,5-difluorophenylmethyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 20 1-[3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[3-(N-{6-methyl-2-nitrophenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(N-{1-methyl-3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{3-(2-furyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[3-(N-{1-methyl-3-phenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane;
- 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane;
- 1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 20 1-[3-(N-{3-(4-*t*-butylphenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.
- 25 More preferred compounds of the present invention are selected from the group consisting of:
- 1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(Azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[4-(1-Piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(1,4,10-Trioxa-7,13-diazacyclopentadecan-7-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 5 1-[4-[4-(2-Pyridyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-[4-(2-Pyrimidyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1,4-Bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride;
- 1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 15 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1-[4-(N-(4-amino-2-methylquinolin-6-yl)aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 20 1-[4-(N-(4-(2-guanidinothiazol-4-yl)phenyl)aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-(3-(2-guanidinothiazol-4-yl)phenyl)aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[5-nitro-3-(N-(3-(2-thienyl)pyrazol-5-yl)aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-(4-(2-guanidinothiazol-4-yl)phenyl)aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[3-(N-(3-(2-guanidinothiazol-4-yl)phenyl)aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-(3-(2-thienyl)pyrazol-5-yl)aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;



- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes
- 20 thereof.

The most preferred compounds included in the present invention are selected from the group consisting of:

- 1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 25 1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane
- 30 pentahydrochloride;
- 1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and
- 15 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

Preferred compounds of formula (II) are selected from the group consisting of:

- 20 1,4-Bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]benzene bis-trifluoroacetic acid salt;
- 2,6-Bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]pyridine bis-trifluoroacetic acid salt; and
- 1,4-Bis[{1-(2-Benzimidazolyl)-1-guanidino}methyl]benzene;
- 25 or further pharmaceutically acceptable salts, hydrates, solvates, esters or metal complexes thereof.

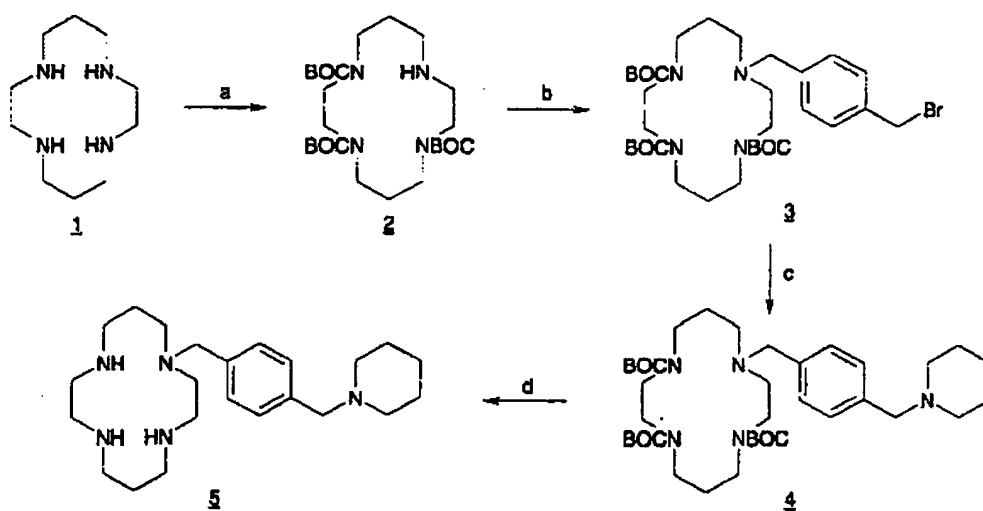
Also included in the present invention are pharmaceutically acceptable salts and complexes. Preferred are the zinc, copper, nickel, cobalt and rhodium complexes, hydrochloride, hydrobromide and trifluoroacetate salts. The compounds of the present

30 invention may contain one or more asymmetric carbon atoms and may exist in racemic and optically active forms. All of these compounds and diastereomers are contemplated to be within the scope of the present invention.

The compounds of Formulas (I) and (II) are prepared as shown in Schemes I to IV below wherein the pendent substituents (X, Z, A, Y', Y<sup>1</sup>, Y<sup>2</sup> and X') are as defined in formulas 1 and 2 and provided that the pendent substituents do not include any such substituents that render inoperative the processes of Schemes I the IV. All of the starting materials are commercially available or are readily made from commercially available starting materials by those of skill in the art.

Compounds of formula I where X represents hydrogen are prepared by methods analogous to that shown in scheme 1.

10

Scheme 1

a) BOC<sub>2</sub>O, CH<sub>2</sub>Cl<sub>2</sub>; b) α,α'-dibromo-*p*-xylene, K<sub>2</sub>CO<sub>3</sub>, MeCN, 60°C; c) piperidine, K<sub>2</sub>CO<sub>3</sub>, MeCN, 60°C; d) HCl, dioxane, CH<sub>2</sub>Cl<sub>2</sub>.

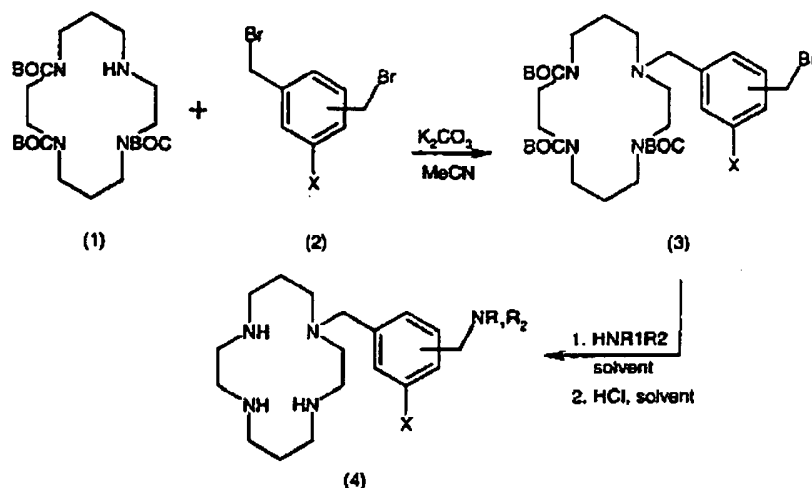
Compound 1, available commercially, is protected as its tri-*tert*-butylcarbamate derivative 2, which is alkylated on the free nitrogen to give compound 3. The benzylic bromide is displaced with the appropriate N nucleophile to give the protected precursor 4, which is deprotected with acid to furnish the final compound 5.

Compounds where the -CH<sub>2</sub>-Z substituent is in the "meta" position can be readily made by the skilled worker, using commercially available starting materials or using materials readily made from commercially available materials by analogous methods.

Compounds of formula I where X is other than hydrogen are prepared by methods analogous to that shown in scheme 2. Further, compounds of formula I where Z represents NY<sup>1</sup>Y<sup>2</sup> are prepared by methods analogous to that shown in scheme 2.

25

Scheme 2

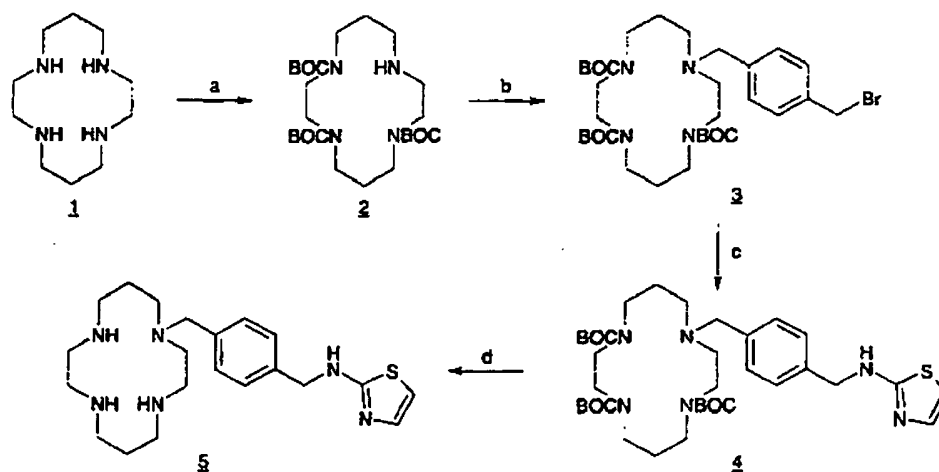


Compound **1**, available commercially, is alkylated with dibromides **2**, prepared by literature methods, in a suitable solvent in the presence of potassium carbonate to give the mono-bromide **3**. **3** was heated with amines  $R^1R^2NH$  (as used in this Scheme,  $R^1R^2$  is  $Y^1Y^2$  of formula 1) in a suitable solvent with or without the addition of a base to give intermediates which were deprotected with HCl to furnish the final compounds **4**.

Compounds where the  $-CH_2-Z$  substituent is in the "meta" position can be readily made by the skilled worker, using commercially available starting materials or using materials readily made from commercially available materials by analogous methods.

Compounds of formula I where Z represents  $NY^1Y^2$  are also prepared by methods analogous to that shown in scheme 3.

### Scheme 3



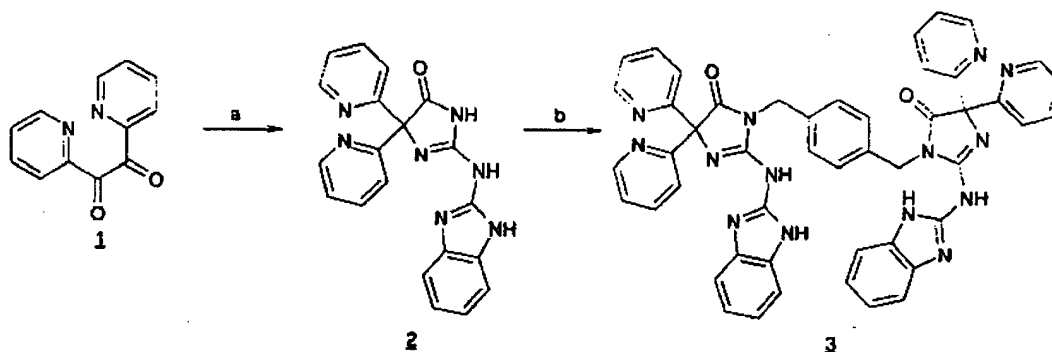
- 15 a)  $BOC_2O$ ,  $CH_2Cl_2$ ; b)  $\alpha,\alpha'$ -dibromo-*p*-xylene,  $K_2CO_3$ , MeCN,  $60^\circ C$ ; c) 2-aminothiazole,  $K_2CO_3$ , MeCN,  $60^\circ C$ ; d) HCl, dioxane,  $CH_2Cl_2$ .

Compound 1, available commercially, is protected as its tri-*tert*-butylcarbamate derivative 2, which is alkylated on the free nitrogen to give compound 3. The benzylic bromide is displaced with the appropriate N nucleophile to give the protected precursor 4, which is deprotected with acid to furnish the final compound 5.

- 5        Compounds where the -CH<sub>2</sub>-Z substituent is in the "meta" position can be readily made by the skilled worker, using commercially available starting materials or using materials readily made from commercially available materials by analogous methods.

10        Compounds of formula (II) are prepared by methods analogous to that shown in scheme 4.

Scheme 4



- 15        a) 2-Guanidinobenzimidazole, NaOH, rt; b)  $\alpha,\alpha'$ -dibromo-p-xylene, DMF, rt Compound 1, available commercially, condenses with 2-guanidinobenzimidazole to give the rearranged product 2, which is converted to its sodium salt and alkylated regioselectively with a bis-electrophile to give compound 3.

20        With appropriate manipulation and protection of any chemical functionality, synthesis of the remaining compounds of Formula (I) and (II) is accomplished by methods analogous to those above and to those described in the Experimental section.

Pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes of the presently invented compounds are readily prepared by those of skill in the art using readily available starting materials.

25        In order to use a compound of the Formula (I) or (II) or a pharmaceutically acceptable salt, hydrate, solvate, ester or metal complex thereof for the treatment of humans and other mammals it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

Because the present compounds have been found to act as CXCR-4 receptor antagonist they are useful for the treatment of diseases including but not limited to bacterial, fungal and protozoan infections, pain, thrombocytopenia, cancer, diabetes, obesity, anorexia, bulimia, asthma, allergies, Parkinson's disease, acute heart failure, hypotension, hypertension, neural damage, atherosclerosis, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers, benign prostatic hypertrophy, migraine, angiogenesis, vomiting, psychotic and neurological disorders (e.g. anxiety, schizophrenia, manic depression, depression, delirium, dementia, mental retardation) and dyskinesias (Huntington's disease and Gilles de la Tourette's syndrome), viral infections, such as HIV infection in patients having clinical signs of AIDS and for the treatment of asymptomatic HIV-infected subjects. The present compounds are also useful for the treatment of an injured or severed spinal cord and other injury-related disease states.

The treatment of thrombocytopenia, as described herein, is accomplished by enhancing the production of platelets.

By the term "co-administering" and derivatives thereof as used herein when directed to the TPO mimetic aspect of this invention is meant either simultaneous administration or any manner of separate sequential administration of a TPO mimetic compound, as described herein, and a further active ingredient or ingredients, known to treat thrombocytopenia, including chemotherapy-induced thrombocytopenia and bone marrow transplantation and other conditions with depressed platelet production. Preferably, if the administration is not simultaneous, the compounds are administered in a close time proximity to each other. Furthermore, it does not matter if the compounds are administered in the same dosage form, e.g. one compound may be administered topically and another compound may be administered orally.

Because the compounds of the present invention have been found to be active as TPO mimetics they exhibit therapeutic utility in treating thrombocytopenia and other conditions with depressed platelet production.

In determining potency as TPO mimetics, the following assays were employed:

#### Luciferase Assay

Compounds of the present invention were tested for potency as mimetics of the TPO receptor in a Luciferase assay such as described in Lamb, et al., Nucleic Acids Research 23: 3283-3289 (1995) and Seidel, et al., Proc. Natl. Acad. Sci., USA 92: 3041-3045 (1995) by substituting a TPO-responsive BaF3 cell line (Vigon et al. Proc. Natl. Acad. Sci. USA 1992, 89, 5640-5644) for the HepG2 cells utilized therein. The murine BaF3 cells express TPO receptors and closely match the pattern of STAT (signal

transducers and activators of transcription) activation observed in primary murine and human bone marrow cells in response to TPO.

Some of the most preferred compounds of this invention were also active in an in vitro proliferation assay using the human UT-7/TPO leukemic megakaryoblastic cell line (Komatsu, N. et al., Blood, 1996, 87, 4552-4560). UT-7/TPO cells express TPO-R and are absolutely dependent on the presence of TPO for growth and survival. Likewise, some of the most preferred compounds of this invention were also positive in stimulating the maturation of megakaryocytes from human bone marrow cells. In this assay, purified human CD34+ progenitor cells were incubated in liquid culture with test compounds for 10 days and the number of cells expressing the transmembrane glycoprotein CD41 (gpIIb), a megakaryocytic marker, was then measured by flow cytometry (see Cwirla, S. E. et al Science, 1997, 276, 1696-1699).

The pharmaceutically active compounds within the scope of this invention are useful as TPO mimetics in mammals, including humans, in need thereof.

Some of the preferred compounds within the scope of the invention showed activation from about 5% to 100% of control (control is the maximal response to TPO) at a concentration of 0.1-30  $\mu$ M in the luciferase assay. The preferred compounds of the invention also promoted the proliferation of UT-7/TPO cells at a concentration of 0.1 to 30  $\mu$ M. The preferred compounds of the invention also showed activity in the CD41 megakaryocytic assay at a concentration of 0.1 to 30  $\mu$ M.

The activity of the compound of Example 46 in the luciferase assay is: 86% of maximal TPO effect with an EC50 of 2.7  $\mu$ M.

One aspect of the present invention therefor provides a method of treating thrombocytopenia and other conditions with depressed platelet production, which comprises administering a compound of Formula (I) or (II), as described above, in a quantity effective to enhance platelet production. The compounds of Formulas (I) and (II) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as TPO mimetics. The drug may be administered to a patient in need thereof by any conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The present invention therefor provides a method of treating thrombocytopenia and other conditions with depressed platelet production, which comprises administering a compound of Formula (I) or (II), as described above, in a quantity effective to enhance platelet production. The compounds of Formulas (I) and (II) also provide for a method of treating the above indicated disease states because of their demonstrated ability to act as TPO mimetics. The drug may be administered to a patient in need thereof by any

conventional route of administration, including, but not limited to, intravenous, intramuscular, oral, subcutaneous, intradermal, and parenteral.

The pharmaceutical preparations are made following conventional techniques of a pharmaceutical chemist involving mixing, granulating, and compressing, when necessary, for tablet forms, or mixing, filling and dissolving the ingredients, as appropriate, to give the desired oral or parenteral products.

Doses of the presently invented pharmaceutically active compounds in a pharmaceutical dosage unit as described above will be an efficacious, nontoxic quantity preferably selected from the range of 0.001 - 100 mg/kg of active compound, preferably 0.001 - 50 mg/kg. When treating a human patient in need of a pharmaceutically active compound of this invention, the selected dose is administered preferably from 1-6 times daily, orally or parenterally. Preferred forms of parenteral administration include topically, rectally, transdermally, by injection and continuously by infusion. Oral dosage units for human administration preferably contain from 0.05 to 3500 mg of active compound. Oral administration, which uses lower dosages is preferred. Parenteral administration, at high dosages, however, also can be used when safe and convenient for the patient.

Optimal dosages to be administered may be readily determined by those skilled in the art, and will vary with the particular active in use, the strength of the preparation, the mode of administration, and the advancement of the disease condition. Additional factors depending on the particular patient being treated will result in a need to adjust dosages, including patient age, weight, diet, and time of administration.

The method of this invention of inducing TPO mimetic activity in mammals, including humans, comprises administering to a subject in need of such activity an effective TPO mimetic amount of a pharmaceutically active compound of the present invention.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use as a TPO mimetic.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use in therapy.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use in enhancing platelet production.

The invention also provides for the use of a compound of Formula (I) or (II) in the manufacture of a medicament for use in treating thrombocytopenia.

The invention also provides for a pharmaceutical composition for use as a TPO mimetic which comprises a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier.



The invention also provides for a pharmaceutical composition for use in the treatment of thrombocytopenia which comprises a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier.

5 The invention also provides for a pharmaceutical composition for use in enhancing platelet production which comprises a compound of Formula (I) or (II) and a pharmaceutically acceptable carrier.

10 In addition, the pharmaceutically active compounds of the present invention can be co-administered with further active ingredients, such as other compounds known to antagonize the CXCR-4 receptor or which exhibit a therapeutic effect on a disease state that is treatable with a CXCR-4 receptor antagonist; or such as other compounds known to treat thrombocytopenia, including chemotherapy-induced thrombocytopenia and bone marrow transplantation and other conditions with depressed platelet production, or compounds known to have utility when used in combination with a TPO mimetic.

15 No unacceptable toxicological effects are expected when compounds of the present invention are administered in accordance with the present invention.

The activity of the compounds of Formula (I) and (II) as antagonists of the CXCR-4 receptor are demonstrated by the following test.

CXCR-4/SDF-1 Assay Protocol

20 Assay plates were seeded with RBL transfected with the SDF-1 receptor. Dye loading buffer (EMEM w/Earl's salts w/ L-glutamine with 1X Sulphinpyrozone and 10% BSA, 100 uL) was added to each well, and the plate incubated for 90 minutes at 37°C. The dye loading buffer was aspirated from the plates. Hydrolysis buffer (EMEM w/Earl's salts w/ L-glutamine with 1X Sulphinpyrozone, 100uL) was added to each well, and the plate incubated for 10 minutes at 37°C. The cells were washed 3 times with wash buffer (1X  
25 Krebs Ringer, 15 mM HEPES, 1mM MgCl, 1 mM CaCl with 1X Sulphinpyrozone and 0.10% gelatin), then wash buffer was dispensed to each well (100uL/well). The plate was incubated for 10 minutes at 37°C, then placed in FLIPR™ (Molecular Devices). Test compounds in gelatin buffer (1X Krebs Ringer, 15 mM HEPES, 1mM MgCl, 1 mM CaCl with 0.10% gelatin, 50uL) were preincubated with cells for 3 minutes, then ligand (SDF-  
30 1alpha/PBSF, 15nM final concentration) was added. The plate was incubated for 2 minutes while continually reading.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following  
35 Examples are, therefore, to be construed as merely illustrative and not a limitation of the scope of the present invention in any way.

Experimental DetailsExample 1Preparation of 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

*a,a'*-Dibromo-*p*-xylene (36.0 g, 136 mmol) was stirred at 60°C in acetonitrile (500 mL) until it dissolved. Potassium carbonate (3.5 g, 25.3 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (6.0 g, 11.98 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2% methanol/dichloromethane) to afford the title compound as a foam (7.4 g, 90 %). MS (ES+) *m/e* 683 and 685 [M+H]<sup>+</sup>.

b) 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (326 mg, 0.477 mmol), 1-acetylpiperazine (95 mg, 0.741 mmol) and anhydrous potassium carbonate (350 mg, 2.53 mmol) in acetonitrile (30 mL) was vigorously stirred together at 50°C for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-3% methanol/dichloromethane) to give the title compound as an oil (300 mg, 86%). MS (ES+) *m/e* 731 [M+H]<sup>+</sup>.

c) 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

To a solution of 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (175 mg, 0.239 mmol) in 1,4-dioxane (1.0 mL) was added a solution of 4M hydrogen chloride in 1,4-dioxane (1.0 mL). The mixture was stood for 2 hours, the white solid collected and washed successively with 1,4-dioxane, diethyl ether and hexane.

The hygroscopic solid was dried *in vacuo* (80°C) to give the title compound (35 mg, 34%). MS (ES+) *m/e* 431 [M+H]<sup>+</sup>

Example 2

Preparation of 1-[4-(1,4-diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting homopiperazine for 1-acetylpiperazine, the title compound was prepared (27% overall). <sup>1</sup>H NMR (300MHz, d3-MeOD/D<sub>2</sub>O) δ 7.67 (d, 2H), 7.50 (d, 2H), 4.52 (s, 2H), 3.98 (s, 2H), 3.90 (s, 2H), 3.62 (m, 2H), 3.53-3.20 (m, 8H), 3.15 (m, 2H), 2.95 (m, 4H), 2.35 (m, 2H), 2.19 (m, 4H), 2.09 (m, 2H), 1.26 (m, 4H).

Example 3

Preparation of 1-[4-(azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting hexamethyleneimine for 1-acetylpiperazine, the title compound was prepared (45% overall). MS (ES+) m/e 402 [M+H]<sup>+</sup>.

Example 4

Preparation of 1-[4-(1-piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting piperidine for 1-acetylpiperazine, the title compound was prepared (75% overall). MS (ES+) m/e 388 [M+H]<sup>+</sup>.

Example 5

Preparation of 1-[4-(1-morpholinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting morpholine for 1-acetylpiperazine, the title compound was prepared (60% overall). <sup>1</sup>H NMR (300MHz, D<sub>2</sub>O) δ 7.7-7.5 (m, 4H), 4.5 (s, 2H), 4.1 (m, 4H), 3.8 (br m, 2H), 3.6-3.0 (br m, 16H), 2.2 (br s, 4H), 1.2 (s, 4H).

Example 6

Preparation of 1-[4-(azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting azacyclotridecane for 1-acetylpiperazine, the title compound was prepared (13% overall). MS (ES+) m/e 522 [M+H+HCl]<sup>+</sup>.

Example 7

Preparation of 1-[4-(5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-yl)methyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 5,6,14,15-dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-diene for 1-acetylpiperazine, the title compound was prepared (42% overall). <sup>1</sup>H NMR (300MHz, d6-DMSO, D<sub>2</sub>O) δ 7.90-6.95(m, 12H), 4.7-4.1 (m, 14H), 3.5 (s, 2H), 3.45 (s, 2H), 3.5-3.0 (br m, 6H), 2.85-2.30 (br m, 2H), 2.3-2.0 (br m, 6H), 1.2 (br s, 6H).

Example 8

Preparation of 1-[4-(1,4,7-trioxo-10-azacyclododecan-10-yl)methyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-aza-12-crown for 1-acetylpiperazine, the title compound was prepared (86% overall). MS (ES+) m/e 478 [M+H]<sup>+</sup>.

Example 9

Preparation of 1-[4-(1,4,7,10-tetraoxa-13-azacyclopentadecan-13-yl)methyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-aza-15-crown-5 for 1-acetylpiperazine, the title compound was prepared (50% overall). MS (ES+) m/e 522 [M+H]<sup>+</sup>.

Example 10

Preparation of 1-[4-(1,4,10-trioxo-7,13-diazacyclopentadecan-7-yl)methyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1,4,10-trioxo-7,13-diaza-cyclopentadecane for 1-acetylpiperazine, the title compound was prepared (21% overall). MS (ES+) m/e 261 [M+2H]<sup>2+</sup>, 557.

Example 11

Preparation of 1-[4-[4-(2-pyridyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-(2-pyridyl)piperazine for 1-acetylpiperazine, the title compound was prepared (24% overall). MS (ES+) m/e 466 [M+H]<sup>+</sup>, 502.

Example 12

Preparation of 1-[4-[4-(2-pyrimidyl)-1-piperazinomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1-(2-pyrimidyl)piperazine for 1-acetylpiperazine, the title compound was prepared (25% overall). MS (ES+) m/e 467 [M+H]<sup>+</sup>, 503.

#### Example 13

5 Preparation of 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

10 A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (293 mg, 0.429 mmol) and 2-guanidinobenzimidazole (225 mg, 1.28 mmol) in acetonitrile (5 mL) was stirred and heated under reflux for 30 min. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-5 % methanol/dichloromethane) to give the title compound as a yellow gum, (115 mg, 34%). MS (ES+) m/e 778 [M+H]<sup>+</sup>.

15 b) 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

To a solution of 1-[4-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (115 mg, 0.148 mmol) in 1,4-dioxane (2.0 mL) was added a 4M solution of hydrogen  
20 chloride in 1,4-dioxane (1.5 mL). The mixture was stood overnight, the red solid collected and washed successively with 1, 4,-dioxane, diethyl ether and hexane. The hygroscopic solid was dried *in vacuo* (80°C) to give the title compound (72 mg, 73%). MS (ES+) m/e 478 [M+H]<sup>+</sup>.

#### Example 14

25 Preparation of 1-[4-(1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting piperazine for 1-acetylpiperazine, the title compound was prepared (32% overall). MS (ES+) m/e 389 [M+H]<sup>+</sup>.

30 Example 15

Preparation of 1,4-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride

a) 1,4-bis-(4-[4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-ylmethyl]phenylmethyl)piperazine

A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (287 mg, 0.449 mmol), piperazine (92 mg, 1.07 mmol) and anhydrous potassium carbonate (100 mg, 0.724 mmol) in acetonitrile (5 mL) was vigorously stirred together at 50°C for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-5 % methanol/dichloromethane) to give the title compound as an oil, (114 mg, 21%).

MS *m/e* 646 [M+2H]<sup>2+</sup>.

b) 1,4-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine decahydrochloride

Following the procedure of Example 1(c), except substituting 1,4-bis-[4-[4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecan-1-ylmethyl]phenylmethyl]piperazine for 1-[4-(4-acetyl-1-piperazinomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane, the title compound was prepared (56%). MS (ES+) *m/e* 346 [M+2H]<sup>2+</sup>.

#### Example 16

Preparation of 1-[4-(1,5-diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

Following the procedure of Example 1(a)-(c), except substituting 1,5-diazacyclooctane dihydrobromide (G. Ewin *et al.*, *J. Chem. Res., Synop.*, 1985, 11, 334) for 1-acetyl-piperazine, the title compound was prepared (6% overall). <sup>1</sup>H NMR (300MHz, d6-DMSO/D<sub>2</sub>O) δ 7.74 (s, 4H), 4.43 (br s, 4H), 3.6-3.0 (br m, 20H), 2.21 (br m, 12H).

#### Example 17

1-(4-[bis[2-(diethylamino)ethyl]aminomethyl]phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride

a) 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

*a,a'*-Dibromo-*p*-xylene (36.0 g, 136 mmol) was stirred at 60°C in acetonitrile (500 mL) until it dissolved. Potassium carbonate (3.5 g, 25.3 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (6.0 g, 11.98 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2%

methanol/dichloromethane) to afford the title compound as a foam (7.4 g, 90 %). MS (ES+)  $m/e$  683 and 685  $[M+H]^+$ .

b) 1-(4-{bis[2-(diethylamino)ethyl]aminomethyl}phenylmethyl)-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

- 5 A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (279 mg, 0.408 mmol), N,N,N',N'-tetraethyldiethylenetriamine (211  $\mu$ L, 0.820 mmol) and anhydrous potassium carbonate (100 mg, 0.724 mmol) in acetonitrile (5 mL) was vigorously stirred together at 50°C for 1 hour. The solvent was evaporated and the residue was purified by flash chromatography (silica gel, 0-5% methanol/dichloromethane) to give the title compound as an oil. (210 mg, 63%)

MS (ES+)  $m/e$  818  $[M+H]^+$ .

c) 1-(4-{bis[2-(diethylamino)ethyl]aminomethyl}phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride

- 15 To a solution of 1-(4-{bis[2-(diethylamino)ethyl]aminomethyl}phenylmethyl)-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (200 mg, 0.244 mmol) in 1,4-dioxane (2.0 mL) was added a 4M solution of hydrogen chloride in diethyl ether (1.5 mL). The mixture was stood overnight, the solid collected and washed successively with diethyl ether and hexane.
- 20 The hygroscopic solid was dried *in vacuo* (80°C) to give the title compound (100 mg, 53%).  $^1\text{H}$  NMR (300MHz,  $d_6$ -DMSO/ $D_2O$ )  $\delta$  7.6 (m, 4H), 4.0-2.9 (br m, 24H), 2.2 (br s, 4H), 1.11 (m, 12H), 1.07 (t, 12H).

#### Example 18

- 25 1-[4-[(2-aminoethyl)(3-aminopropyl)aminomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane heptahydrochloride

a) (2-phthalimidoethyl)(3-phthalimidoprop-1-yl)amine

- A mixture of N-(2-aminoethyl)-1,3-propanediamine (10.0 mL, 79.2 mmol), phthalic anhydride (24.6 g, 166 mmol) and *p*-toluenesulfonic acid (1.0 g, 5.26 mmol) in toluene (500 mL) was stirred and heated under reflux, using a Dean & Stark head, for 5 hours. The mixture was cooled and diluted with hexane. The solid was collected, washed with ether and hexane, and dried to give the title compound as a pale yellow solid (21 g, 72%). MS (ES+)  $m/e$  378  $[M+H]^+$ .

b) 1-[4-[(2-phthalimidoethyl)(3-phthalimidoprop-1-yl)amino]methyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(a)-1(c), except substituting (2-phthalimidoethyl)(3-phthalimidoprop-1-yl)amine for N,N,N',N'-tetraethyldiethylenetriamine, the title compound was prepared (58% overall). MS (ES+) m/e 341 [M+2H]<sup>2+</sup>.

- 5 c) 1-(4-[(2-aminoethyl)(3-aminopropyl)amino]methyl)phenylmethyl)-1,4,8,11-tetraazacyclotetradecane heptahydrochloride  
1-[4-[(2-phthalimidoethyl)(3-phthalimidoprop-1-yl)amino]methyl]phenylmethyl)-1,4,8,11-tetraazacyclotetradecane pentahydrochloride (200 mg, 0.234 mmol) in ethanol (5 mL) was treated with hydrazine hydrate (2.0 mL, 64.2 mmol) and stirred at 60°C for 4  
10 hours. The solvent was evaporated and the residue was slurried in diethyl ether with potassium carbonate. The mixture was filtered and the filtrate treated with a 4M solution of HCl in 1,4-dioxane and this mixture allowed to stand overnight. The solid was collected, washed with diethyl ether and hexane, then dried *in vacuo* (80°C) to give the title compound (150 mg, 95 %). MS (ES+) m/e 456 [M+HCl+H]<sup>+</sup>.

15 Example 19

1-[4-[di-(2-pyridyl)aminomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

- a) 1-[4-[di-(2-pyridyl)aminomethyl]phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane  
20 2,2'-Dipyridylamine (77 mg, 0.500 mmol) was added to a suspension of sodium hydride (18.8 mg of a 60% dispersion in mineral oil, 0.470 mmol) in anhydrous DMF (10 mL) and the mixture stirred at 25°C for 1 hour under nitrogen. A solution of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (292 mg, 0.427 mmol) in anhydrous DMF was added and the  
25 mixture stirred overnight. Water was added and the mixture extracted twice with diethyl ether and once with ethyl acetate. The combined organic extracts were washed with water, dried (anhydrous potassium carbonate) and evaporated to a yellow gum, which was purified by flash chromatography (silica gel, 0-5% methanol/dichloromethane) to give the title compound as an oil, (100 mg 30%). MS (ES+) m/e 774 [M+H]<sup>+</sup>.

- 30 b) 1-[4-[di-(2-pyridyl)aminomethyl]phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

Following the procedure of Example 1(c), except substituting 1-[4-[di-(2-pyridyl)aminomethyl]phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane for 1-(4-{bis[2-(diethylamino)ethyl]aminomethyl}phenylmethyl)-



4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane, the title compound was prepared (94%). MS (ES+) *m/e* 474 [M+H]<sup>+</sup>.

#### Example 20

1-[4-(2-thiazolylaminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane  
5 pentahydrochloride

Following the procedure of Example 17(a)-1(c), except 2-aminothiazole for N,N,N',N'-tetraethyldiethylenetriamine, the title compound was prepared (19% overall). MS (ES+) *m/e* 202 [M+2H]<sup>2+</sup>.

#### Example 21

10 1,4-bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]benzene bis-trifluoroacetic acid salt

a) 2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-5H-imidazolin-4-one

A mixture of 2,2'-pyridil (15.8 g, 74.4 mmol) and 2-guanidinobenzimidazole (19.5 g, 111.7 mmol) in methanol (440 mL) was treated with a solution of sodium hydroxide  
15 (2.97 g, 74.4 mmol) in water (74 mL) and the resulting mixture was left standing at room temperature for 4 days. A crystalline material was filtered and the mother liquor allowed to stand for 3 weeks. The precipitated solid was filtered and dried under vacuum to give the title compound (10.5 g, 36%) as its sodium salt. <sup>1</sup>H NMR (300MHz, d<sub>6</sub>-DMSO) δ 11.55 (br s, 1H), 10.05 (br s, 1H), 8.47 (m, 2H), 7.76 (m, 2H), 7.68 (m, 2H), 7.25 (m, 4H), 6.90  
20 (m, 2H). Further slow concentration of the mother liquor gave a third solid, which was filtered and dried under vacuum to give the title compound (1.25g, 5%) as a solid. <sup>1</sup>H NMR (300MHz, d<sub>6</sub>-DMSO) δ 11.8 (br s, 2H), 10.5 (br s, 1H), 8.64 (m, 2H), 7.89 (m, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.44 (m, 4H), 7.07 (m, 2H).

b) 1,4-bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-4H-imidazolin-3-ylmethyl]benzene bis-trifluoroacetic acid salt  
25

To a solution of 2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-5H-imidazolin-4-one (390 mg, 1.00 mmol) in DMF (1 mL) at room temperature was added α,α'-dibromo-p-xylene (120 mg, 0.45 mmol) in one portion. The reaction was stirred at room temperature for 12 hours then concentrated under reduced pressure. The residue was taken up in DMSO  
30 (5 mL) and purified by reverse phase HPLC [ODS, 0-90% CH<sub>3</sub>CN/H<sub>2</sub>O (0.1% TFA)] to give the title compound as a yellow solid (240 mg, 50%) MS (ES+) *m/e* 841 [M+H]<sup>+</sup>.

#### Example 22

2,6-bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]pyridine bis-trifluoroacetic acid salt

Following the procedure of Example 21(a)-1(b), except substituting 2,6-bis(bromomethyl)pyridine for  $\alpha,\alpha'$ -dibromo-p-xylene, the title compound was prepared (2% overall). MS (ES+) m/e 842 [M+H]<sup>+</sup>.

#### Example 23

##### 5 1,4-bis{[1-(2-benzimidazolyl)-1-guanidino]methyl}benzene

To a solution of 2-guanidinobenzimidazole (350 mg, 2.0 mmol) in DMF at 0°C was added NaH (88 mg of a 60 % dispersion in mineral oil, 2.2 mmol) in portions over five minutes. The solution was warmed to room temperature and allowed to stir for 45 minutes. The solution was cooled to 0°C and  $\alpha,\alpha'$ -dibromo-p-xylene (264 mg, 1.0 mmol) was added  
 10 in portions over 1 hour. The solution was stirred an additional hour, concentrated under reduced pressure, and taken up in ethyl acetate. The organic solution was washed with aqueous NH<sub>4</sub>Cl, NaCl, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, ethyl acetate) to give the title compound as a white powder (350 mg, 77%). MS (ES+) m/e 453 [M+H]<sup>+</sup>.

#### 15 Example 24

##### 1-[3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

20  $\alpha,\alpha'$ -Dibromo-*m*-xylene (22.0 g, 83.3 mmol) was stirred at 60°C in acetonitrile (350 mL) until it dissolved. Potassium carbonate (2.0 g, 14.5 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (4.0 g, 7.99 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially  
 25 evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2% methanol/dichloromethane) to afford the title compound as a foam (4.55 g, 83 %). <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>)  $\delta$  7.30-7.19 (m, 4H), 4.49 (s, 2H), 3.51 (s, 2H), 3.45-3.20 (m, 12H), 2.62 (m, 2H), 2.38 (m, 2H), 1.91 (m, 2H), 1.68 (m, 2H), 1.47-1.43 (m, 27H).

30 b) 1-[3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-4,8,11-tri(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

A mixture of 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (293 mg, 0.43 mmol), 2-guanidinobenzimidazole (225 mg, 1.287 mmol) and potassium carbonate (100 mg, 0.724 mmol) were heated together  
 35 under reflux with vigorous stirring in acetonitrile (5 mL) for 1 hr. Flash chromatography

(silica gel, dichloromethane to 4% methanol/ dichloromethane) gave the title compound (115 mg, 34%) as a yellow gum. MS (ES+) m/e 778 [M+H]<sup>+</sup>.

c) 1-[3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

5 A solution of 1-[3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-4,8,11-tri(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (70 mg, 0.090 mmol) in ethanol (2 mL) was treated with HCl in dioxane (4M, 2.0 mL, 8.0 mmol) and stood overnight. The solid was filtered, washed with dioxane, ether and hexane to give the title compound (50 mg, 84%) as a red solid. MS (ES+) m/e 478 [M+H]<sup>+</sup>.

#### 10 Example 25

1-[4-(2-aminobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

15 *α,α'*-Dibromo-*p*-xylene (36.0 g, 136 mmol) was stirred at 60°C in acetonitrile (500 mL) until it dissolved. Potassium carbonate (3.5 g, 25.3 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (6.0 g, 11.98 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially  
20 evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2% methanol/dichloromethane) to afford the title compound as a foam (7.4 g, 90 %). MS (ES+) m/e 683 and 685 [M+H]<sup>+</sup>.

b) 1-[4-(2-aminobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane  
25 pentahydrochloride

The procedure described in example 24b and 1c was followed here, using 2-aminobenzimidazole in place of 2-guanidinobenzimidazole and 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane in place of 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri(*t*-  
30 butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane, to give the title compound as a solid. MS (ES+) m/e 219 [M+2H]<sup>2+</sup>.

#### Example 26

1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide

35 a) 4,11-bis(*p*-toluenesulfonyl)-1,8-bis-[4-(4,8,11-tris(*p*-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane

- A mixture of slightly impure 4,8,11-tris-(p-toluenesulfonyl)-1,4,8,11-tetraazacyclotetradecane (590 mg, 0.890 mmol) (M. Ciampolini *et. al.*, *Inorg. Chem.*, 1987, 26, 3527), *a,a'*-dibromo-*p*-xylene (117 mg, 0.445 mmol), potassium carbonate (369 mg, 2.67 mmol) and acetonitrile (10 mL) was heated at 80 °C for 18h, then cooled and partitioned between water and dichloromethane. Extracts were washed (saturated aqueous NaCl), dried (MgSO<sub>4</sub>) and solvent removed under vacuum. The crude material was chromatographed (silica gel, 50-100% ethyl acetate/ hexane then 5% methanol/dichloromethane) to give the title compound (35 mg, 8%) as an amorphous solid. MS (ES+) *m/e* 1019 [M+2H]<sup>2+</sup>.
- b) 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide
- 4,11-bis(p-toluenesulfonyl)-1,8-bis-[4-(4,8,11-tris{p-toluenesulfonyl}-1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane (35 mg, 0.017 mmol) was heated under reflux in 48% aqueous HBr/acetic acid (2:3, 2.5 mL) for 18h. After cooling, the solid was filtered, washed (acetic acid, dichloromethane, ether) and dried (60°C under vacuum) to give the title compound (26 mg, 87%) as a pink solid. MS (ES+) *m/e* 403 [M+2H]<sup>2+</sup>.

#### Example 27

- 1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide

The procedure described in example 26 also gave the title compound (8 mg, 2%) as a solid. <sup>1</sup>H NMR (300MHz, D<sub>2</sub>O) δ 7.57 (d, 4H, J = 7.9Hz), 7.47 (d, 4H, J = 7.9Hz), 4.29 (s, 4H), 4.03 (s, 4H), 3.39-2.94 (m, 48H), 2.13 (m, 8H), 1.97 (m, 4H).

#### Example 28

- 1-[4-(N-[3-(methylamino)propyl]-N-methylaminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride

- The procedure described in example 24b and 1c was followed here, using N,N'-dimethyl-1,3-propanediamine in place of 2-guanidinobenzimidazole and 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane in place of 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane, to give the title compound as a solid. <sup>1</sup>H NMR (300 MHz, DMSO/D<sub>2</sub>O) δ 7.8 (m, 4H), 4.4 (m, 4H), 3.6 (s, 6H), 3.4-2.9 (m, 14H), 2.65 (m, 4H), 2.15 (m, 8H).

#### Example 29

- 1-[4-(N-[3,4-methylenedioxyphenylmethyl]aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

A mixture of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (61 mg, 0.089 mmol) and 3,4-methylenedioxybenzylamine (40 mg, 0.267 mmol) in ethanol (3 mL) was heated at 80-90°C for 3 hours. The solvent was evaporated and the residue redissolved in DMSO and chromatographed by preparative HPLC (20-80 % acetonitrile/water + 0.1 % TFA). The resulting purified tri-(*t*-butoxycarbonyl) intermediate was dissolved in ethanol (2.5 mL) and HCl in dioxane (4.0M, 2.0 mL, 8 mmol) added. The mixture was allowed to stand for 24 h, then evaporated to give the title compound. MS (ES+) *m/e* 454 [M+H]<sup>+</sup>.

#### Examples 30 to 34

The following compounds were prepared according to the procedure described in example 29 using the appropriate amines:

1-[4-(N-{3,5-difluorophenylmethyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) *m/e* 446 [M+H]<sup>+</sup>.

1-[4-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) *m/e* 502 [M+H]<sup>+</sup>.

1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) *m/e* 476 [M+H]<sup>+</sup>.

1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) *m/e* 536 [M+H]<sup>+</sup>.

1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) *m/e* 536 [M+H]<sup>+</sup>.

#### Example 35

1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[3-(bromomethyl)-5-nitrophenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

The procedure described in example 1a was followed here, using 1,3-bis(bromomethyl)-5-nitrobenzene in place of *o,o'*-dibromo-*m*-xylene, to give the title compound as a foam. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 8.12 (m, 2H), 7.65 (s, 1H), 4.53 (s, 2H), 3.63 (s, 2H), 3.5-3.2 (m, 12H), 2.65 (m, 2H), 2.40 (m, 2H), 1.92 (m, 2H), 1.70 (m, 2H), 1.55-1.30 (m, 27H).

b) 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

The procedure described in example 29 was followed here, using 1-[3-(bromomethyl)-5-nitrophenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane in place of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane and 5-amino-3-(2-thienyl)pyrazole in place of 3,4-methylenedioxybenzylamine, to give the title compound as a solid. MS (ES+)  $m/e$  513 [M+H]<sup>+</sup>.

#### Examples 36 to 39

The following compounds were prepared according to the procedure described in example 35 using the appropriate amines:

1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+)  $m/e$  547 [M+H]<sup>+</sup>.

1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+)  $m/e$  521 [M+H]<sup>+</sup>.

1-[3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+)  $m/e$  581 [M+H]<sup>+</sup>.

1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+)  $m/e$  581 [M+H]<sup>+</sup>.

#### Example 40

1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[5-bromo-3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

The procedure described in example 1a was followed here, using 5-bromo-1,3-bis(bromomethyl)benzene in place of *a,a'*-dibromo-*m*-xylene, to give the title compound as a foam. MS (ES+)  $m/e$  761, 763, 765 [M+H]<sup>+</sup>.

b) 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

The procedure described in example 29 was followed here, using 1-[5-bromo-3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane in place of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-

butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane and 5-amino-3-(2-thienyl)pyrazole in place of 3,4-methylenedioxybenzylamine, to give the title compound as a solid. MS (ES+) m/e 546, 548 [M+H]<sup>+</sup>.

#### Examples 41 to 44

- 5 The following compounds were prepared according to the procedure described in example 40 using the appropriate amines:

1-[5-bromo-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) m/e 580, 582 [M+H]<sup>+</sup>.

10

1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) m/e 554, 556 [M+H]<sup>+</sup>.

15

1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) m/e 614, 616 [M+H]<sup>+</sup>.

1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) m/e 614, 616 [M+H]<sup>+</sup>.

#### Example 45

- 20 1-[3-(N-{6-methyl-2-nitrophenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

The procedure described in example 29 was followed here, using 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane in place of 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane and 6-methyl-2-nitroaniline in place of  
25 3,4-methylenedioxybenzylamine, to give the title compound as a solid. MS (ES+) m/e 455 [M+H]<sup>+</sup>.

#### Example 46

- The following compounds were prepared according to the procedure described in example  
30 45 using the appropriate amines:

1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. MS (ES+) m/e 468 [M+H]<sup>+</sup>.

#### Example 47

1-[4-(N-{1-methyl-3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

5        *a,a'*-Dibromo-*p*-xylene (36.0 g, 136 mmol) was stirred at 60°C in acetonitrile (500 mL) until it dissolved. Potassium carbonate (3.5 g, 25.3 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et. al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (6.0 g, 11.98 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially  
10        evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2% methanol/dichloromethane) to afford the title compound as a foam (7.4 g, 90 %). MS (ES+) *m/e* 683 and 685 [M+H]<sup>+</sup>.

b) 1-[4-(N-{1-methyl-3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

15        A mixture of 5-amino-1-methyl-3-(2-thienyl)pyrazole (300 mg, 1.67 mmol), 1-[4-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (379 mg, 0.555 mmol) and ethanol (3 mL) was heated under reflux for 3 h, then cooled. The solvent was removed under vacuum and the residue  
20        purified by preparative HPLC (ODS, 10-90% acetonitrile/water + 0.1%TFA). A solution of the protected intermediate obtained in 4M HCl/dioxane (2 mL, 8 mmol) and dichloromethane (4 mL) was allowed to stand 18 h, then filtered. The residue was washed with dichloromethane and ether, then dried under high vacuum to give the title compound (20 mg, 5%) as a solid. LCMS *m/z* 482 [M+H]<sup>+</sup>.

25        Examples 48 to 50

The following compounds were prepared according to the procedure described in example 47 using the appropriate amines:

30        1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. LCMS *m/z* 400 [M+H]<sup>+</sup>.

1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. LCMS *m/z* 476 [M+H]<sup>+</sup>.

35        1-[4-(N-{3-(2-furyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride. LCMS *m/z* 452 [M+H]<sup>+</sup>.

Example 51



1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

a) 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane

5            *a,a'*-Dibromo-*m*-xylene (22.0 g, 83.3 mmol) was stirred at 60°C in acetonitrile (350 mL) until it dissolved. Potassium carbonate (2.0 g, 14.5 mmol) was added, followed by the dropwise addition of a solution of 1,4,8-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (B. Boitrel *et al.*, *Tetrahedron Lett.*, 1995, 36, 4995) (4.0 g, 7.99 mmol) in acetonitrile (100 mL). The mixture was stirred for 6 hours, cooled and partially

10            evaporated. The excess dibromoxylene was filtered off, the mother liquors evaporated under vacuum and chromatographed (silica gel, 50% dichloromethane/hexane to 2% methanol/dichloromethane) to afford the title compound as a foam (4.55 g, 83 %). <sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>) δ 7.30-7.19 (m, 4H), 4.49 (s, 2H), 3.51 (s, 2H), 3.45-3.20 (m, 12H), 2.62 (m, 2H), 2.38 (m, 2H), 1.91 (m, 2H), 1.68 (m, 2H), 1.47-1.43 (m, 27H).

15            b) 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride

                 A mixture of 5-amino-3-(4-methylphenyl)pyrazole (217 mg, 1.25 mmol), 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (779 mg, 1.14 mmol), potassium carbonate (473 mg, 3.42 mmol)

20            and acetonitrile (11 mL) was stirred at 60°C for 2.5 h, then cooled and partitioned between water and ethyl acetate. The extracts were washed with water, saturated aqueous NaCl, then dried (MgSO<sub>4</sub>). The solvent was removed under reduced pressure and the residue chromatographed (silica gel, ethyl acetate, then 10% methanol/dichloromethane + 0.5% aqueous ammonia). A solution of 30 mg of the protected intermediate obtained in 4M

25            HCl/dioxane (1 mL, 4 mmol) and dichloromethane (2 mL) was allowed to stand 18 h, then filtered. The residue was washed with dichloromethane and ether, then dried under high vacuum to give the title compound (25 mg, 26%) as a solid. MS (ES<sup>+</sup>) *m/e* 476 [M+H]<sup>+</sup>.

Example 52

1-[3-(N-{1-methyl-3-phenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane

30            A solution of 5-amino-1-methyl-3-phenylpyrazole (51 mg, 0.292 mmol) and 1-[3-(bromomethyl)phenylmethyl]-4,8,11-tri-(*t*-butoxycarbonyl)-1,4,8,11-tetraazacyclotetradecane (100 mg, 0.146 mmol) in dimethylformamide (0.5 mL) was shaken for 18 h then partitioned between 0.1 M aqueous potassium carbonate and ethyl

35            acetate. The organic extract was evaporated under reduced pressure and the residue purified by RP preparative HPLC (ODS, 10-90% acetonitrile/water + 0.1% TFA). A solution of the protected intermediate obtained in 4M HCl/dioxane (1 mL, 4 mmol) and

dichloromethane (3 mL) was allowed to stand 72 h, then diluted with dichloromethane and water. The aqueous layer was partitioned between 1M aqueous NaOH and dichloromethane. The organic layer was dried (sodium sulfate) and evaporated under reduced pressure to give the title compound (3 mg, 4%) as an amorphous solid. LCMS m/z 476 [M+H]<sup>+</sup>.

#### Examples 53 to 55

The following compounds were prepared according to the procedure described in example 52 using the appropriate amines:

1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane. . LCMS m/z 510, 512 [M+H]<sup>+</sup>.

1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane.. LCMS m/z 538 [M+H]<sup>+</sup>.

1-[3-(N-{3-(4-*t*-butylphenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane... LCMS m/z 532 [M+H]<sup>+</sup>.

Formulations for pharmaceutical use incorporating compounds of the present invention can be prepared in various forms and with numerous excipients. Examples of such formulations are given below.

#### Example 56

##### Inhalant Formulation

A compound of Formula I or II, (1 mg to 100 mg) is aerosolized from a metered dose inhaler to deliver the desired amount of drug per use.

#### Example 57

##### Tablet Formulation

##### Tablets/Ingredients

##### Per Tablet

1.	Active ingredient (Cpd of Form. I or II)	40 mg
2.	Corn Starch	20 mg
3.	Alginic acid	20 mg
4.	Sodium Alginate	20 mg
5.	Mg stearate	1.3 mg

##### Procedure for tablet formulation:

Ingredients 1, 2, 3 and 4 are blended in a suitable mixer/blender. Sufficient water is added portion-wise to the blend with careful mixing after each addition until the mass is of a consistency to permit its conversion to wet granules. The wet mass is converted to granules by passing it through an oscillating granulator using a No. 8 mesh (2.38 mm) screen. The wet granules are then dried in an oven at 140°F (60°C) until dry. The dry granules are lubricated with ingredient No. 5, and the lubricated granules are compressed on a suitable tablet press.

#### Example 58

##### Parenteral Formulation

A pharmaceutical composition for parenteral administration is prepared by dissolving an appropriate amount of a compound of Formula I or II in polyethylene glycol with heating. This solution is then diluted with water for injections Ph Eur. (to 100 ml). The solution is then rendered sterile by filtration through a 0.22 micron membrane filter and sealed in sterile containers.

Specific Examples of formulations for pharmaceutical use incorporating compounds of the present invention are given below.

#### Example 59 - Capsule Composition

An oral dosage form for administering a presently invented compound is produced by filling a standard two piece hard gelatin capsule with the ingredients in the proportions shown in Table II, below.

Table II

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride (Compound of Example 32)	25 mg
Lactose	55 mg
Talc	16 mg
Magnesium Stearate	4 mg

#### Example 60 - Injectable Parenteral Composition

An injectable form for administering a presently invented agonist of the TPO receptor is produced by stirring 1.5% by weight of 1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane

pentahydrochloride (Compound of Example 39) in 10% by volume propylene glycol in water.

### Example 61 - Tablet Composition

5

The sucrose, calcium sulfate dihydrate and a presently invented agonist of the TPO receptor, as shown in Table III below, are mixed and granulated in the proportions shown with a 10% gelatin solution. The wet granules are screened, dried, mixed with the starch, talc and stearic acid, screened and compressed into a tablet.

10

Table III

<u>INGREDIENTS</u>	<u>AMOUNTS</u>
1-[3-(N-{6-methyl-2-nitrophenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride (Compound of Example 45)	20 mg
calcium sulfate dihydrate	30 mg
sucrose	4 mg
starch	2 mg
talc	1 mg
stearic acid	0.5 mg

Preferred among the compounds of the present invention are compounds of Examples 2 - CXCR4, 7 - CXCR4, 34 - TPO, 39 - TPO, 40 - TPO, 44 - TPO and 51 - TPO.

15

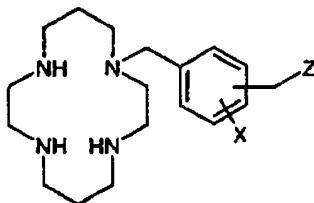
Most preferred among the compounds of the present invention are compounds of Examples 13 - CXCR4, 33 - TPO, 35 - TPO, 43 - TPO, 46 - TPO and 49 - TPO, 53 - TPO.

20

While the preferred embodiments of the invention are illustrated by the above, it is to be understood that the invention is not limited to the precise instructions herein disclosed and that the right to all modifications coming within the scope of the following claims is reserved.

What is claimed is:

1. A compound according to formula (I):



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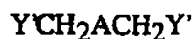
Formula (I)

wherein:

- the  $-\text{CH}_2\text{-Z}$  substituent is meta or para to the tetraazacyclotetradecane substituent;  
 Z represents a nitrogen-linked heteroaryl, a substituted nitrogen-linked heteroaryl, a  
 cyclic amine moiety, a substituted cyclic amine moiety, or  $\text{NY}^1\text{Y}^2$  where  $\text{Y}^1$  and  
 10  $\text{Y}^2$  are each independently selected from hydrogen, alkyl, substituted alkyl,  $\text{C}_3\text{-C}_{12}$ aryl,  
 $\text{C}_3\text{-C}_{12}$ aryl, substituted  $\text{C}_3\text{-C}_{12}$ aryl, cycloalkyl, and substituted cycloalkyl; and  
 X is selected from the group consisting of hydrogen, alkyl,  $\text{C}_3\text{-C}_{12}$ aryl, substituted  
 $\text{C}_3\text{-C}_{12}$ aryl, amino, alkylamino, nitro, hydroxy, alkoxy, halogen, carboxyl and  
 carboxamido; and  
 15 pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes  
 thereof.

2. A compound according to formula (II):

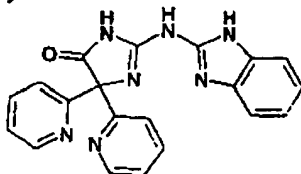
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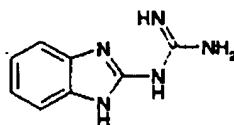
Formula (II)

wherein,

$\text{Y}'$  represents a moiety selected from



and



wherein the Y' moiety can be optionally substituted by a substituent selected from the group consisting of alkyl, alkoxy, halogen and carboxy; and

A represents an X'-substituted aryl or heteroaryl ring wherein X' is selected from the group consisting of hydrogen, alkyl, aryl, amino, alkylamino, nitro, hydroxy, alkoxy, halogen, carboxyl, and carboxamido;

provided that the YCH<sub>2</sub> groups are arranged meta or para to each other; and

pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

3. A compound according to claim 1 selected from the group consisting of :

1-[4-(4-Acetyl-1-piperazinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

1-[4-(Azacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1-Piperidinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1-Morpholinomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

1-[4-(1,4,7-Trioxa-10-azacyclododecan-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1,4,7,10-Tetraoxa-13-azacyclopentadecan-13-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

1-[4-(1,4,10-Trioxa-7,13-diazacyclopentadecan-7-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

- 1-{4-[4-(2-Pyridyl)-1-piperazinomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-{4-[4-(2-Pyrimidyl)-1-piperazinomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 5 1-{4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl}-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-{4-(1-Piperazinomethyl)phenylmethyl}-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1,4-Bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]piperazine
- 10 decahydrochloride;
- 1-{4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl}-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-{4-[Bis[2-(diethylamino)ethyl]aminomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane heptahydrochloride;
- 15 1-{4-[[2-(2-Aminoethyl)(3-aminopropyl)amino]methyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane heptahydrochloride;
- 1-{4-[Di-(2-pyridyl)aminomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-{4-(2-Thiazolylaminomethyl)phenylmethyl}-1,4,8,11-tetraazacyclotetradecane
- 20 pentahydrochloride;
- 1-{3-(2-guanidinobenzimidazol-1-ylmethyl)phenylmethyl}-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-{4-(2-aminobenzimidazol-1-ylmethyl)phenylmethyl}-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1-{4-[N-(3-(methylamino)propyl)-N-methylaminomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 30 1-{4-[N-[3,4-methylenedioxyphenylmethyl]aminomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-{4-[N-[3,5-difluorophenylmethyl]aminomethyl]phenylmethyl}-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[4-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 20 1-[5-bromo-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 25 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{6-methyl-2-nitrophenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and
- 30 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{1-methyl-3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;



- 1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[4-(N-{3-(2-furyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{1-methyl-3-phenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane;
- 10 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane;
- 1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 15 1-[3-(N-{3-(4-*t*-butylphenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.
- 20 4. A compound according to claim 3 selected from the group consisting of:
- 1,8-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 1,11-bis-[4-(1,4,8,11-tetraazacyclotetradecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane dodecahydrobromide;
- 25 1-[4-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-nitro-3-(phenothiazin-10-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;

- 1-[3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)-5-nitrophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 5 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{4-amino-2-methylquinolin-6-yl}aminomethyl)-5-bromophenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 10 1-[5-bromo-3-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 15 1-[4-(N-{3-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 20 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 1-[3-(N-{1,3-diphenylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- 25 further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

5. A compound according to claim 2 selected from the group consisting of:
- 1,4-Bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]benzene bis-trifluoroacetic acid salt;
- 30 2,6-Bis[2-(2-benzimidazolylamino)-5,5-di(2-pyridyl)-4-oxo-5H-imidazolin-3-ylmethyl]pyridine bis-trifluoroacetic acid salt; and
- 1,4-Bis[[1-(2-Benzimidazolyl)-1-guanidino]methyl]benzene; and

further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

6. A compound according to claim 3 selected from the group consisting of:

- 5 1-[4-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 1-[4-(N-{3-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 1-[5-nitro-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 10 1-[5-bromo-3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 1-[5-bromo-3-(N-{4-(2-guanidinothiazol-4-yl)phenyl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 15 1-[3-(N-{3-(2-thienyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 1-[4-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
  - 1-[3-(N-{3-(4-methylphenyl)pyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and
  - 20 1-[3-(N-{3-(4-chlorophenyl)-1-methylpyrazol-5-yl}aminomethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane; and
- further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

25

7. A compound according to claim 6 selected from the group consisting of:

- 1-[4-(1,5-Diazacyclooctan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;
- 1-[4-(2-Guanidinobenzimidazol-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride;
- 30 1-[4-(5,6,14,15-Dibenzo-1,4-dioxo-8,12-diazacyclopentadeca-5,14-dien-8-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride;

1-[4-(Azacyclotridecan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane pentahydrochloride; and

1-[4-(1,4-Diazacycloheptan-1-ylmethyl)phenylmethyl]-1,4,8,11-tetraazacyclotetradecane hexahydrochloride; and

- 5 further pharmaceutically acceptable salts, hydrates, solvates, esters and metal complexes thereof.

8. A method of antagonizing a CXCR-4 receptor by administering a compound according to claim 1.

10

9. A method of antagonizing a CXCR-4 receptor by administering a compound according to claim 2.

10. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a compound according to claim 1.

15

11. A pharmaceutical composition comprising a suitable pharmaceutical carrier and a compound according to claim 2.

12. A compound according to any one of claims 1 to 7 for use as an active therapeutic substance.

20

13. Use of a compound according to claim 1 in the manufacture of a medicament for use in treating thrombocytopenia.

25

14. Use of a compound according to claim 2 in the manufacture of a medicament for use in treating thrombocytopenia.

15. A method of agonizing the TPO receptor in a subject which comprises administering an effective amount of a compound according to claim 1.

30

16. A method of agonizing the TPO receptor in a subject which comprises administering an effective amount of a compound according to claim 2.

17. Use of a compound according to claim 1 in the manufacture of a medicament for use in antagonizing the CXCR-4 receptor.

18. Use of a compound according to claim 2 in the manufacture of a  
5 medicament for use in antagonizing the CXCR-4 receptor.

19. A method of treating a CXCR-4-mediated disease comprising administering to a patient in need of treatment a safe and effective amount of a compound according to claim 1 or claim 2.

10

20. A method according to claim 8 or claim 9 wherein the disease is selected from the group consisting of bacterial, fungal and protozoan infections, pain, cancer, thrombocytopenia, diabetes, obesity, anorexia, bulimia, asthma, allergies, Parkinson's disease, acute heart failure, hypotension, hypertension, neural damage, atherosclerosis, urinary retention, osteoporosis, angina pectoris, myocardial infarction, stroke, ulcers,  
15 benign prostatic hypertrophy, migraine, angiogenesis, vomiting, psychotic and neurological disorders, dyskinesias, viral infections, and spinal cord-related injury.

21. A method according to claim 19 wherein the disease is a neurological  
20 disease selected from the group consisting of anxiety, schizophrenia, manic depression, depression, delirium, dementia, mental retardation, Huntington's disease and Gilles de la Tourette's syndrome.

22. A method according to claim 19 wherein the disease is a viral infection  
25 selected from HIV infection exhibiting clinical signs of AIDS and asymptomatic HIV infection.

23. A method according to claim 19 wherein the disease is an injury to the spinal cord.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/11951

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/33, 31/415, 31/425, 31/44, 31/445, 31/47, 31/495, 31/50, 31/535, 31/54, 31/55, 31/555; C07D 225/00, 235/04, 257/02, 401/14  
US CL : 514/183, 184, 218, 225.8, 236.2, 252.13, 252.14, 253.01, 313, 326, 333, 340, 370, 395, 406; 540/465, 474;

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : Please See Continuation Sheet

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)  
CAS ONLINE

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,817,807 A (BRIDGER et al.) 06 October 1998, examples 1-12.	1, 8, 10, 12, 17, 19 and 22
X	BRIDGER et al., Synthesis and Structure - Activity Relationships of Phenylenebis(methylene)-Linked Bis-tetraazamacrocycles That Inhibit Human Immunodeficiency Virus Replication. 2. Effect of Heteroaromatic Linkers on the Activity of Bicyclams, Journal of Medicinal Chemistry, January 1996, Vol. 39, No. 1, pages 109-119, especially pages 109-111.	1, 8, 10, 12, 17, 19 and 22
X	US 5,583,131 A (BRIDGER et al.) 10 December 1996, see entire document.	1, 3, 4, 8, 10, 12, 17, 19 and 22
X	JOAO et al., Quantitative Structural Activity Relationship Study of Bis-Tetraazacyclic Compounds. A Novel Series of HIV-1 and HIV-2 Inhibitors, Journal of Medicinal Chemistry, September 1995, Vol. 38, No. 19, pages 3865-3873, especially pages 3866-3867.	1, 3, 4, 8, 10, 12, 17, 19 and 22
X	BRIDGER et al., Synthesis and Structure - Activity Relationships of Phenylenebis(methylene)-Linked Bis-Tetraazamacrocycles That Inhibit HIV Replication. Effects of Macrocyclic Ring Size and Substituents on the Aromatic Linker, Journal of Medicinal Chemistry, January 1995, Vol. 38, No. 2, pages 366-378, especially page 368.	1, 3, 4, 8, 10, 12, 17, 19 and 22

☒ Further documents are listed in the continuation of Box C.



See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier applications or patents published on or after the international filing date

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T"

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"X"

document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y"

document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"Z"

document member of the same patent family

Date of the actual completion of the international search

10 July 2000 (10.07.2000)

Date of mailing of the international search report

15 AUG 2000

Name and mailing address of the ISA/US

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# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/11951

## C (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MALLIK et al., Synthetic Bis-Metal Ion Receptors for Bis-Imidazole "Protein Analogs", Journal of the American Chemical Society, October 1994, Vol. 116, No. 20, pages 8902-8911, especially page 8904.	1 and 10
X	DE CLERCQ et al., Highly Potent and Selective Inhibition of Human Immunodeficiency Virus by the Bicyclam Derivative JM3100, Antimicrobial Agents and Chemotherapy, April 1994, Vol. 38, No. 4, pages 668-674, especially page 670.	1, 3, 4, 8, 13, 12, 17, 19 and 22
X	MALLIK et al., Selective Recognition of Bis-Imidazoles by Complementary Bis-Metal Ion Complexes, Journal of the American Chemical Society, March 1993, Vol. 115, No. 6, pages 2518-2520.	1, 3, 4 and 10
X	HELPS et al., General Routes For The Synthesis of Mono, Di and Tri-N-Substituted Derivatives of Cyciam, Tetrahedron, 1989, Vol. 45, No. 1, pages 219-226, especially page 220.	1 and 10
X	CIAMPOLINI et al., Dinickel and Dicopper Complexes with N,N-Linked Bis(cyclam) Ligands. An Ideal System for the Investigation of Electrostatic Effects on the Redox Behavior of Pairs of Metal Ions, Inorganic Chemistry, October 1987, Vol. 26, No. 21, pages 3527-3533, especially pages 3527-3528.	1, 3, 4 and 10

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/11951

## Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claim Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐  
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.



# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/11951

**BOX II. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING** This application contains the following inventions or groups of inventions which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1, 3, 4, 6-8, 10, 12, 13, 15, 17 and 19-23, drawn to the compounds, compositions and method of use of the compounds of formula I.

Group II, claim(s) 2, 5, 9, 11, 12, 14, 16 and 18-23, drawn to the compounds, compositions and method of use of the compounds of formula II.

The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the compounds of formula I and the compounds of formula II do share a special technical feature.

Continuation of B. **FIELDS SEARCHED** Item 1: 514/183, 184, 218, 225.8, 236.2, 252.13, 252.14, 253.01, 313, 326, 333, 340, 370, 395, 406; 540/465, 474; 546/256; 548/305.4

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